Progression in melanoma

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Progression in Melanoma
Considerations and Implications in Dissecting Nodal Fields

Kevin P. Wevers
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Progression in Melanoma
Considerations and Implications in Dissecting Nodal Fields

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Chapter 1

General introduction and outline of thesis

Cutaneous melanoma

Cutaneous melanoma, which is the most malignant skin cancer type, has got one of the fastest increasing incidence rates of all cancers in the western world. In the Netherlands, its incidence has more than doubled over the past two decades, from 11.3 per 100,000 in 1989 to 28.1 per 100,000 in 2010.[1, 2] In 2013, roughly 5000 people in the Netherlands and 70,000 in the United States of America will be diagnosed with melanoma.[1] Although nearly half of these patients will present with thin melanomas (Breslow thickness < 1.0mm)[3], one out of every five patients will die due to progression of their cutaneous melanoma.[1]

Staging

Most melanoma patients initially present with clinically localized disease (stage I and II). The most important predictors of outcome in such patients are Breslow thickness, ulceration, and the mitotic rate of the primary tumor.[3, 4] The sentinel lymph node status, determined by sentinel lymph node biopsy (SLNB), is also of great importance for prognosis and in most studies this represents the strongest predictor of outcome.[5] These pathologic characteristics form the backbone of the 7th melanoma staging manual developed by the American Joint Committee on Cancer (AJCC) in 2009 (Table 1 and 2).[3]

Melanomas most frequently metastasize to the regional lymph nodes, before distant sites become involved.[6] When metastases in regional lymph nodes are found, either by SLNB (micrometastases) or by analysis of a clinically palpable lymph node (macrometastases), the patient is classified as stage III. Stage IV melanoma describes metastatic disease at distant sites, categorized according to location of metastasis and serum Lactate Dehydrogenase (LDH) level.

Treatment of the primary cutaneous melanoma

Local treatment for the primary melanoma consists of surgical excision with melanoma free margins. The recommended margin of a therapeutic re-excision depends on the Breslow thickness of the melanoma and amounts 1 cm for melanoma < 2.0 mm and 2 cm for melanoma > 2.0 mm.[7]

Table 1. TNM staging categories for cutaneous melanoma

Tumor	**Breslow thickness**	**Ulceration / mitotic rate**
T1	≤1.0 mm	T1a: Without ulceration and mitosis <1/mm^2
		T1b: With ulceration and mitosis ≥1/mm^2
T2	1.01-2.0 mm	T2a: Without ulceration T2b: With ulceration
T3	2.01-4.0 mm	T3a: Without ulceration T3b: With ulceration
T4	>4.0 mm	T4a: Without ulceration T4b: With ulceration
Node	**No. of metastatic nodes**	**Nodal metastatic burden***
N0	0	
N1	1	N1a: Micrometastasis N1b: Macrometastasis
N2	2-3	N2a: Micrometastases N2b: Macrometastases N2c: In transit metastases/ satellites without metastatic nodes
N3	4+ metastatic nodes, matted nodes, or in transit metastases/satellites with metastatic nodes	
Metastasis	**Site**	**Serum LDH**
M0	No distant metastasis	
M1a	Distant skin, subcutaneous, or nodal metastases	Normal LDH
M1b	Lung metastases	Normal LDH
M1c	All other visceral metastases Any distant metastasis	Normal LDH Elevated LDH

* Micrometastases are diagnosed through sentinel lymph node biopsy. Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2. Anatomic stage groupings for melanoma

	Clinical Staging*				Pathologic Staging*		
	T	**N**	**M**		**T**	**N**	**M**
IA	T1a	N0	M0	**IA**	T1a	N0	M0
IB	T1b	N0	M0	**IB**	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	**IIA**	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	**IIB**	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	**IIC**	T4b	N0	M0
III	Any T	N1-3	M0	**IIIA**	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	**IV**	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases. Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Sentinel lymph node biopsy and completion lymph node dissection

Because cutaneous melanomas predominantly progress through draining afferent lymph vessels and corresponding lymph nodes (Figure 1), a lot of research is focused on removing occult metastases in regional lymph nodes by dissection of the nodal basin.

Elective regional lymph node dissection for localized melanoma without clinical evidence of metastatic spread was abandoned in the nineties, as it resulted in substantial morbidity (wound infections, seroma, and lymphedema) and increased survival only in one out of five patients who had nodal micrometastasis.[8] Searching for a way to identify these patients with clinically occult nodal metastasis, D.L. Morton introduced the SLNB for melanoma[9] and studied it in the first Multicenter Selective Lymphadenectomy Trial (MSLT-I). The SLNB uses a radioactive tracer and a blue dye to identify the lymph node in the regional lymph node basin to which the cutaneous afferent lymphatic vessels drain first and which is most likely the first site to contain metastases (Figure 2).[10-12] Awaiting the final results after completion of the MSLT-I follow-up, it was already shown that the sentinel node status is a very important prognostic factor in patients with clinically localized melanoma.[5, 13] Moreover, the last interim analysis of the MSLT-I suggested that SLNB, followed by immediate completion lymph node dissection (CLND) if micrometastases are found, leads to an improved melanoma specific survival.[14] Until the final results of MSLT-I are available, most countries use the SLNB as a staging procedure in patients with melanomas > 1 mm Breslow thickness or < 1 mm in case of present ulceration or high mitotic rate.

In sentinel-node positive patients, it is currently recommended to perform a CLND.[15] However, metastatic involvement in so called non-sentinel nodes is found in only 20% on histopathological analysis of the CLND specimens. In other words, roughly 4 out of 5 patients will not have affected regional nodes apart from the positive sentinel node. CLND in these patients causes unnecessary morbidity and economic burden. Currently pending international trials are studying alternative treatment regimens for sentinel-node positive patients. The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) by Morton et al.[16] compares CLND with nodal observation using ultrasound and performing a therapeutic lymph node dissection (TLND) only if nodal metastases become clinically manifest. The EORTC MINITUB registration study[17] explores the efficacy of CLND omission in patients with minimal tumor burden in the sentinel node.

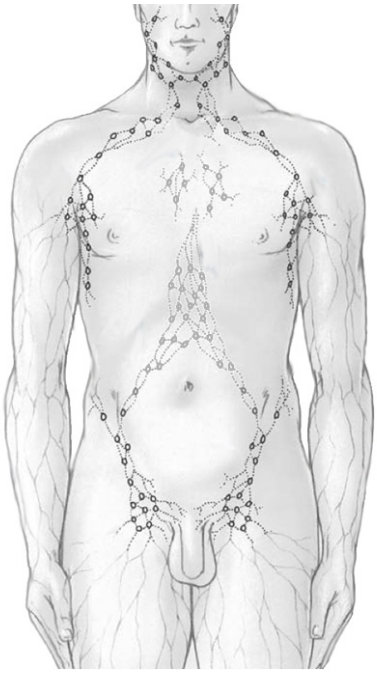

Figure 1. Draining lymph node basins in groin, axilla, and neck
(source: Dutch Cancer Society)

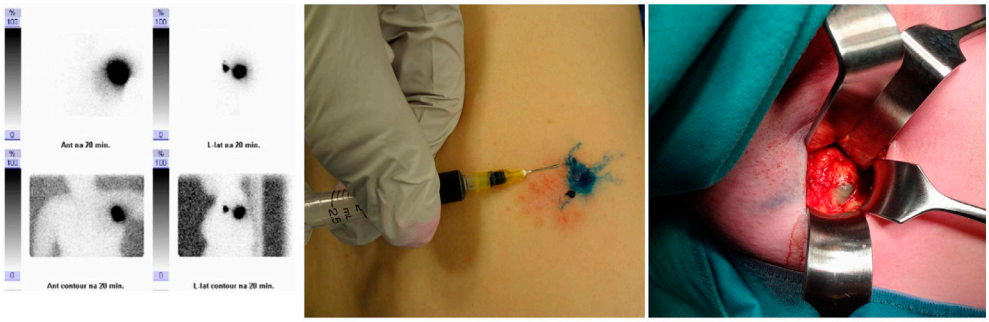

Figure 2. Lymphoscintigraphy and intracutaneous injection of blue dye to identify and remove the sentinel lymph node

Follow-up

The overall prevalence of cancer patients continues to increase due to rising incidence rates and improved treatment outcomes. Also in melanoma, this has resulted in a rising demand on health care resources with more and more patients needing treatment and subsequent follow-up visits.[18] The frequency of follow-up visits has been widely debated for melanoma, but neither scientific evidence nor international consensus does exist. Overall, high frequency follow-up is currently recommended in countries with the highest melanoma incidence.[19] In order to establish an evidence based follow-up schedule for melanoma patients, our center prospectively studies the feasibility and safety of a reduced follow-up schedule in the pending multicenter MELFO trial.[20, 21]

Nodal and distant metastases

Unfortunately, 16–28% of melanoma patients develop recurrent disease. These recurrences occur locally or in-transit in 20–28%, distant in 15–50%, but most frequently in regional lymph nodes (26–60%).[6] In case of a clinically manifest recurrence in the regional lymph node basin, whole-body FDG/PET and / or spiral CT scanning increase the accurateness of staging by 27% upstaging to stage IV disease.[22] Patients in whom metastatic spread is radiographically limited to the regional lymph nodes (stage IIIB-C) can be treated by a therapeutic lymph node dissection with curative intent. The overall 5-year survival of these patients is 29–52%.[3, 8, 23-26]

Melanoma patients who develop distant metastases (stage IV) suffer a very poor prognosis. The one-year survival rate varies between 33% and 66%, depending on LDH level and the location of the metastases.[3] Different treatment strategies are possible.

In previous studies, the best survival rates were found for stage IV patients who underwent complete surgical removal, i.e. total resection of all radiographic and clinical evident metastases. Small retrospective series established that patients in whom complete surgical removal is feasible have a 5-year survival rate of 15-28%[27-32], which is superior to 5-10% found for patients who receive systemic medical therapy[33, 34]. The prospective series of the Southwest Oncology Group showed a

25% 5-year survival in 64 patients who had their metastases completely resected[35]. Even better survival rates were found during the MMAIT-IV trial which combined surgery with immunotherapy: 5-year survival 40-45%[36]. These results suggest that surgery should be the first choice of treatment for stage IV melanoma whenever complete surgical removal is feasible. However, recent breakthroughs in systemic medical therapy with ipilimumab and BRAF inhibitors like vemurafenib have also shown some promising results.[37, 38] Recently, a randomized controlled trial was initiated to compare complete surgical removal and systemic medical therapy as initial treatment for completely resectable stage IV melanoma.[39]

Biomarkers in melanoma

In general, tumor biomarkers can be used for primary screening, as a diagnostic tool, for staging, as a prognostic marker, to evaluate the effect of treatment, and to screen for recurrences in follow-up. In melanoma, two biomarkers have been extensively studied: earlier LDH and lately S-100B.[40] LDH was implemented in the AJCC system in 2001 only to classify stage IV patients. The melanoma associated molecule S-100B was found to be correlated with melanoma progression in both stage III and IV disease.[41, 42] However, in the United States the biomarker S-100B is rarely used in melanoma research and not widely accepted in melanoma care. In contrast, in Europe the marker, which seems to reflect tumor load[43], is increasingly being studied and used in clinical practice.

OUTLINE

Cutaneous melanoma is characterized by the unbelievably unpredictable arise of distant metastases. However, in contrast to most solid tumors, melanomas show an orderly and predictable nodal metastatic pattern. Improvements in the balance between radical surgical removal of potentially affected lymph nodes and the substantial morbidity and costs this surgery entails should be sought in better patient selection. First, the incidence of and risk factors for complications in ilio-inguinal lymph node dissections in both sentinel node positive patients and patients with palpable nodal metastases are described (chapter 2). Then, *Part I – Predictive factors that enable patient selection for completion lymph node dissection* focuses on the selection of high risk sentinel-node positive patients for CLND using histopathologic characteristics and melanoma biomarkers.

The increasing prevalence of melanoma patients causes a rising demand on healthcare resources. This leads to a stunning increase in follow-up visits, as high-frequency follow-up is practiced in many countries. *Part II – Melanoma follow-up and prognostic factors in surgery for nodal recurrences* discusses medical specialists' opinions on optimal melanoma follow-up and reveals prognostic factors that could improve staging and patient selection for (neo)adjuvant therapies in patients with palpable nodal recurrences. This accurate patient selection is needed in order to apply new systemic medical agents as (neo)adjuvant therapies, without inducing excessive morbidity and costs.

Part III – Feasibility of complete resection in stage IV melanoma studies the proportion of melanoma patients in which complete surgical resection of all distant metastases at stage IV diagnosis is achievable.

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Chapter 2

Early mobilization after ilio-inguinal lymph node dissection for melanoma does not increase the wound complication rate

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ABSTRACT

Aim. Ilio-inguinal lymph node dissection for stage III melanoma is accompanied by a substantial amount of wound complications. Our treatment protocols changed in time in terms of postoperative bed rest prescriptions, being in chronological order Group A: 10 days with a Bohler Braun splint, Group B: 10 days without splint, and Group C: 5 days without splint. The aim of this study was to evaluate the effect of bed rest prescriptions on wound complications.

Methods. For this study, we included all patients who underwent ilio-inguinal dissection for stage III melanoma in the period 1989-2011. Both univariate and multivariable analysis were performed to identify factors that were associated with occurrence of wound complications defined as wound infection, wound necrosis, and seroma.

Results. Of the 204 patients analyzed, 99 suffered one or more wound complications: 51 wound infection, 29 wound necrosis, and 39 seroma. A wound complication occurred in 26 out of 64, 51 out of 89, and 22 out of 51 patients for Group A, B, and C, respectively. Univariate analysis showed age >55 (p=0.001) and presence of comorbidity (p=0.002) to be associated with higher incidence of wound complications. The 5 day bed rest protocol used in group C did not significantly increase the incidence of wound complications (ref=Group A: OR=1.18; 95%CI=0.52-2.68, p=0.698).

Conclusion. Early mobilization did not significantly increase the overall wound complication rate after ilio-inguinal lymph node dissection for melanoma. Age >55 and comorbidity were risk factors in univariate analysis.

Introduction

The incidence of melanoma is constantly increasing in the western world. In the Netherlands the incidence doubled in the past two decades, from 11.3 per 100 000 in 1989 to 26.3 per 100 000 in 2009.[1, 2] Most of the patients present initially with Stage I or II melanoma.[3] Unfortunately, despite defined surgical treatment of the primary melanoma with excision margins of 1 or 2 cm, approximately 16-28% will develop recurrent disease. These recurrences occur in 20-28% local or in-transit, 15-50% on distant sites, but most frequently in regional lymph nodes (26-60%).[4]

For nodal metastases in the groin region, ilio-inguinal lymph node dissection is performed. Both clinically detectable nodal metastases (macrometastasis) and a positive sentinel lymph node biopsy (micrometastasis) identified by hematoxylin and eosin staining reflect nodal disease and are indications for an ilio-inguinal lymph node dissection in our center. These procedures for stage III melanoma are accompanied by a substantial amount of wound complications, with complication rates up to almost 50% in literature.[5-8]

Our treatment protocols for ilio-inguinal lymph node dissection changed in time in terms of postoperative bed rest prescriptions. In the beginning a 10 day long period of strict bed rest with the usage of a Bohler Braun splint was thought to prevent complications by reducing edema and tension along the wound. Later, with the introduction of adjustable hospital beds the Bohler Braun splint was abandoned, although the duration of prescribed bed rest remained 10 days. In this period more wound healing problems seemed to occur[7]. The protocol was adjusted to prescription of 5 days of bed rest in the most recent period following studies that successfully handled early mobilization[6, 9]. Grounds for this adjustment were increasing cost effectiveness as well as the conviction 10 days of bed rest would not improve wound healing and could increase the risk for complications like deep venous thrombosis and pulmonary embolism. This resulted in three consecutive cohorts being in chronological order Group A: 10 days with a Bohler Braun splint, Group B: 10 days without splint, and Group C: 5 days without splint. The aim of this study was to evaluate the effect of bed rest prescriptions on early wound complications.

Patients and methods

Patients and data acquisition

For this retrospective study we included all patients who underwent ilio-inguinal dissection for stage III melanoma for both clinically detectable macrometastasis and micrometastasis found by sentinel node biopsy in our center during the period 1989 to 2011. Patients who underwent a superficial dissection solely or in whom additional adjuvant limb perfusion was performed were excluded. Eventually, 204 melanoma patients were analyzed in present study.

Characteristics of patient, primary melanoma, operative procedure, and postoperative period were recorded. Early wound complications were defined as complications within 30 days of the operative procedure and were divided into wound infection, wound necrosis and seroma. Wound

infection was scored if the wound was opened to drain an abscess, antibiotics were administered, or a positive culture was found. Wound necrosis was defined as necrotic edges of the wound which necessitated secondary wound healing for closure. Seroma was recorded when a puncture was performed.

Surgical procedure

For ilio-inguinal dissection, the superficial lymph nodes as well as the iliac and obturator lymph nodes were excised via a single ellipse shaped incision. The sartorius muscle was used to cover the neurovascular femoral bundle, as described extensively in the past.[7, 10] Since 2004, a single gift of antibiotic prophylaxis was given before the procedure to patients in whom sentinel node biopsy was performed previously. This was introduced to handle the increased risk for wound infection that was found in patients in whom lymph node dissection was performed after sentinel lymph node biopsy.[11]

All patients were ordered strict bed rest with flexion in hip and knee for a minimum of 5 days, depending on the applicable protocol at time of surgical procedure. Flexion in hip and knee in all patients was provided by the Bohler Braun splint or later by the adjustable hospital beds. Support stockings were used for mobilization during the first 6 months and low molecular weight heparin was given until the patient was completely mobilized. Drains were removed after 10 days when the production was less than 20 ml a day. For patients with 5 days of bed rest drains were mostly removed in the outpatient department.

Statistical analysis

Frequencies and percentages were used for description of patient and group characteristics. Differences between bed rest groups A, B, and C were analyzed by Fischer's exact test or the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables, all on a 5% significance level. Association of variables with early complications was assessed by univariate and multivariable logistic regression analyses. All variables significant on a 20% significance level in univariate analysis were entered in the multivariable analysis to identify factors that were independently associated with early complications with a $p<0.050$.

Results

In total, we studied 204 patients, consisting of 105 females and 99 males with a median age of 56 (range 5-91) years. The indication for ilio-inguinal dissection was clinically detected macrometastasis in 152 cases and metastasis found by sentinel lymph node biopsy in 52 patients. More than half of patients (n=110) had a Body Mass Index (BMI) over 25, 58 patients were smokers, and 12 had Diabetes Mellitus. (Table 1)

As shown in table 2, differences in the bed rest groups were the median operative time, the operation year, and median hospital stay. The median time of procedures for patients in Group C was 165 (range 110-290) minutes versus 130 (range 40-280) and 150 (range 75-290) minutes (p<0.001) for patients in Group A and B, respectively.

The median hospital stay was significantly shorter in group C, being 7 (range 5-22) days compared to 14.5 (range 7-34) days in group A and 13 (range 8-45) days in group B (p<0.001). There were no statistically significant differences between the three groups for age, gender, smoking, BMI, diabetes mellitus, total comorbidity, and indication for the procedure.

Table 1. Patient characteristics of 204 ilio-inguinal lymph node dissections for stage III melanoma

Characteristic	n	(%)
Gender		
Male	99	(48.5)
Female	105	(51.5)
Age, in years, median (range)	56	(5-91)
Breslow thickness (mm)		
T1: ≤1.00	18	(8.8)
T2: 1.01-2.0	49	(24.0)
T3: 2.01-4.0	68	(33.3)
T4: >4.0	49	(24.0)
Unknown primary	20	(9.9)
Median mm, (range)	2.5	(0.7-20.0)
Ulceration		
Present	74	(36.3)
Absent	97	(47.5)
Unknown	33	(16.2)
Indication for dissection		
Macrometastasis	152	(74.5)
Micrometastasis	52	(25.5)
Side of dissection		
Left	100	(49.0)
Right	104	(51.0)
Risk factors		
BMI > 25	110	(53.9)
Smoking	58	(28.4)
Diabetes mellitus	12	(5.9)
Comorbidity	60	(29.4)

Abbreviation: BMI, body mass index

Early wound complications

Overall, 99 patients suffered one or more wound complications. A wound infection occurred in 51 patients, wound necrosis was seen in 29 patients, and a seroma puncture was performed in 39 patients.

One or more wound complications occurred in 26 out of 64, in 51 out of 89, and in 22 out of 51 patients for Group A, B, and C (p=0.085), respectively. Multivariable analysis revealed age >55 (OR=2.25; 95%CI=1.19-4.25, p=0.01) and bed rest Group B (ref=Group A: OR=2.72; 95%CI=1.32-5.61, p=0.007) to be independently associated with occurrence of one or more wound complications. The rate of one or more complications in Group C did not significantly differ from the reference Group A (OR=1.18; 95%CI=0.52-2.68, p=0.698). (Table 3) There were no significant differences for occurrence of wound infections and seroma in the bed rest groups. Wound necrosis was most frequently seen in Group B. (Table 3)

In multivariable analysis, higher BMI was associated with the occurrence of wound infections (p=0.018). For wound necrosis, the bed rest group was the only factor associated in multivariable analysis, showing more wound necrosis in Group B (p=0.004). No variable was significantly associated with occurrence of seroma in multivariable analysis. (Table 3)

Table 2. Comparison of clinicopathological characteristics between bed rest groups

Characteristic	Group A 10 days + Bohler		Group B 10 days		Group C 5 days		p
Age							
Median (range)	54	(20-80)	54	(22-86)	60	(5-91)	0.172
≤ 55	33	(51.6)	47	(52.8)	18	(35.3)	
> 55	31	(48.4)	42	(47.2)	33	(64.7)	
Gender							
Male	30	(46.9)	45	(50.6)	27	(52.9)	0.877
Female	34	(53.1)	44	(49.4)	24	(47.1)	
Smoking							
-	44	(68.8)	65	(73.0)	37	(72.5)	0.832
+	20	(31.3)	24	(27.0)	14	(27.5)	
BMI							
Median (range)	25.9	(18.7-39.1)	25.4	(18.6-38.1)	25.2	(13.5-53.9)	0.724
< 25	25	(39.1)	37	(43.5)	25	(49.0)	
25-30	28	(43.8)	34	(40.0)	16	(31.4)	
> 30	9	(14.1)	14	(16.5)	9	(17.6)	
Unknown	2	(3.1)	4	(4.5)	1	(2.0)	
Diabetes mellitus							
-	61	(95.3)	86	(96.6)	45	(88.2)	0.138
+	3	(4.7)	3	(3.4)	6	(11.8)	
Comorbidity							
-	43	(67.2)	66	(74.2)	35	(68.6)	0.607
+	21	(32.8)	23	(25.8)	16	(31.4)	
Indication							
Macrometastasis	46	(71.9)	70	(78.7)	36	(70.6)	0.484
Micrometastasis	18	(28.1)	19	(21.3)	15	(29.4)	
Operative time, min							
Median (range)	130	(40-280)	150	(75-290)	165	(110-290)	**<0.001**
≤ 150 min	41	(64.1)	46	(51.7)	22	(43.1)	
> 150 min	23	(35.9)	43	(48.3)	29	(56.9)	
Surgeon							
Fellow	38	(59.4)	63	(70.8)	21	(41.2)	**0.003**
Staff	26	(40.6)	26	(29.2)	30	(58.8)	
Operation year							
1989-2000	59	(92.2)	27	(30.3)	0	(0)	**<0.001**
2001-2005	5	(7.8)	43	(48.3)	2	(3.9)	
2006-2011	0	(0)	19	(21.3)	49	(96.1)	
Hospital stay							
Median (range)	14.5	(7-34)	13	(8-45)	7	(5-22)	**<0.001**

Abbreviation: BMI, body mass index

Table 3. Univariate and multivariable analysis of characteristics associated with postoperative complications

Characteristic	One or more complications			Wound infection			Wound necrosis			Seroma		
	n / total n (%)	p	Multivariable analysis p OR (95%CI)	n / total n (%)	p	Multivariable analysis, p OR (95%CI)	n / total n (%)	p	Multivariable analysis p OR (95%CI)	n / total n (%)	p	Multivariable analysis p OR (95%CI)
Age			**0.012**			0.179						0.141
≤ 55	36/98 (36.7)	**0.001**	**1**	19/98 (19.4)	0.075	1	12/98 (12.2)	0.438		14/98 (14.3)	0.092	1
> 55	63/106 (63.6)		**2.25 (1.19-4.25)**	32/106 (30.2)		1.62 (0.80-3.27)	17/106 (16.0)			25/106 (23.6)		1.73 (0.83-3.60)
Gender												
Male	50/99 (50.5)	0.584		27/99 (27.3)	0.467		16/99 (16.2)	0.440		19/105 (18.1)	0.702	
Female	49/105 (46.7)			24/105 (22.9)			13/105 (12.4)			20/99 (20.2)		
Smoking									0.246			
-	71/146 (48.6)	0.964		40/146 (27.4)	0.210		17/146 (11.6)	0.095	1	31/146 (21.2)	0.223	
+	28/58 (58.3)			11/58 (19.0)			12/58 (20.7)		1.73 (0.69-4.35)	8/58 (13.8)		
BMI			0.149			**0.018**			0.162			
< 25	34/87 (39.1)	0.055	1	13/87 (14.9)	**0.003**	**1**	7/87 (8.0)	0.065	1	17/87 (19.5)	0.553	
25-30	45/78 (57.7)		1.91 (0.98-3.72)	26/78 (33.3)		**2.60 (1.21-5.59)**	14/78 (17.9)		2.22 (0.78-6.26)	17/78 (21.8)		
> 30	17/32 (53.1)		1.63 (0.69-3.87)	12/32 (37.5)		**3.25 (1.27-8.29)**	6/32 (18.8)		3.12 (0.87-11.16)	4/32 (12.5)		
Diabetes mellitus			0.734									0.082
-	99/192 (47.4)	0.195	1	48/192 (25.0)	1.000		28/192 (14.6)	0.548		34/192 (17.7)	**0.041**	1
+	8/12 (66.7)		1.27 (0.32-5.13)	3/12 (25.0)			1/12 (8.3)			5/12 (41.7)		2.96 (0.87-10.02)
Comorbidity			0.085			0.315			0.103			
-	60/144 (41.7)	**0.002**	1	31/144 (21.5)	0.076	1	17/144 (11.8)	0.127	1	25/144 (17.4)	0.323	
+	39/60 (65.0)		1.96 (0.91-4.21)	20/60 (33.3)		1.45 (0.70-3.01)	12/60 (20.0)		2.16 (0.86-5.46)	14/60 (23.3)		
Indication												
Micrometastasis	24/52 (46.2)	0.691		16/52 (30.8)	0.266		9/52 (17.3)	0.459		7/52 (13.5)	0.230	
Macrometastasis	75/152 (49.3)			35/152 (23.0)			20/152 (13.2)			32/152 (21.1)		
Operative time												
≤ 150 min	51/109 (46.8)	0.594		26/109 (23.9)	0.685		14/109 (12.8)	0.548		19/109 (17.4)	0.512	
> 150 min	47/99 (50.5)			25/95 (26.3)			15/95 (15.8)			20/95 (21.1)		
Surgeon												
Fellow	63/122 (51.6)	0.278		33/122 (27.0)	0.410		19/122 (15.6)	0.498		24/122 (19.7)	0.806	
Staff	36/82 (43.9)			18/82 (22.0)			10/82 (12.2)			15/82 (18.3)		
Operation year									0.421			
1989-2000	39/86 (45.3)	0.304		17/86 (19.8)	0.333		14/86 (16.3)	0.117	1	18/86 (20.9)	0.780	
2001-2005	29/50 (58.0)			14/50 (28.0)			10/50 (20.0)		0.58 (0.19-1.79)	8/50 (16.0)		
2006-2011	31/68 (45.6)			20/68 (29.4)			5/68 (7.4)		0.37 (0.08-1.78)	13/68 (19.1)		
Bed rest group			**0.013**						**0.004**			
A: 10 days + Bohler	26/64 (40.6)	0.085	**1**	13/64 (20.3)	0.395		6/64 (9.4)	**0.002**	**1**	12/64 (18.8)	0.712	
B: 10 days	51/89 (57.3)		**2.72 (1.32-5.61)**	22/89 (24.7)			21/89 (23.6)		**6.46 (1.82-22.93)**	19/89 (21.3)		
C: 5 days	22/51 (43.1)		**1.18 (0.52-2.68)**	16/51 (31.4)			2/51 (3.9)		**1.22 (0.13-11.28)**	8/51 (15.7)		

Abbreviation: BMI, body mass index

Discussion

In the present study, early mobilization after 5 days following ilio-inguinal dissection for stage III melanoma did not increase the wound complication rate. We found both 10 days bed rest without usage of a Bohler Braun splint and age above 55 years to be associated with a higher occurrence of one or more wound complications. The early complication rate of 99 out of 204 found in this study is within the range of complication rates reported in literature for ilio-inguinal dissections.[5-8]

Bed rest protocols

Bed rest of 10 days with usage of a Bohler Braun splint was associated with the lowest overall complication rate: in group A 26 out of 64 patients had one or more complications. The most recent 5 day bed rest regimen currently used in our center (group C) did not show a significant increase, compared to group A, in early wound complication rate (22 out of 51 patients; OR=1.18; 95%CI=0.52-2.68). A 10 day bed rest without the usage of a splint (group B) resulted in a significantly higher complication rate compared to group A (51 out of 89 patients; OR=2.72 95%CI=1.32-5.61). (Table 3) The higher complication rate found for group B was mostly formed by the high rate of wound necrosis in this group, with unknown cause. Although the exact reasons for the differences in complication rates are not clear, they seem to justify mobilization of melanoma patients 5 days after ilio-inguinal dissection.

Other risk factors

The increased risk for wound infections with a high BMI is well known for many surgical procedures as well as for groin dissections in melanoma patients.[12-14] The wound infection rate in this study was increased in patients who had overweight (BMI > 25) and was even higher in patients who were obese (BMI > 30). In patients with a sentinel node biopsy preceding the ilio-inguinal dissection, 16 out of 52 suffered a wound infection compared to 35 out of 152 patients operated on for a macrometastasis (p=0.266). This wound infection rate for patients operated on for a positive sentinel node was not reduced despite of the perioperative antibiotic prophylaxis administered since 2004 in our center.[11] The wound necrosis rate was significantly lower in the 5 day bed rest group. Seroma was more frequently seen in diabetic patients (34 out of 192 vs 5 out of 12 in non-diabetics), although this was only significant in univariate analysis.

Future perspectives

The results of this study show that reducing the prescribed days of bed rest from 10 to 5 days after ilio-inguinal dissection for melanoma is feasible and does not significantly increase the early wound complication rate. Moreover, a 5 day bed rest regimen was associated with a significantly shorter hospital stay and could therefore contribute to increase cost-effectiveness of this surgical procedure. Moreover, early mobilization of patients will reduce morbidity related to prolonged immobility

(like venous thromboembolic events), although our cohort was too small to study these specific complications. In the future, even further reducing bed-rest and hospital day could be explored. Because no scientific data is available, we would recommend studying complication rates after 3 days of bed rest, before further reducing bed rest protocols. In our opinion a Bohler Braun splint is obsolete and patients often experience discomfort. Therefore we discourage its use in future practice.

Limitations

Limitations of this study are associated with its retrospective character. Although complications seen in the outpatient department within 30 days were included in the analysis, there could have been under-registration of minor complications, especially in the 5 day bed rest group. Maybe, this phenomenon accounts for the differences in wound necrosis rates between group B and C.

Some other centers may already mobilize their patients after 3, 2, or even one day, which could make the results of the present study not applicable to their situation. However, we feel that reducing bed rest to only 3 or less days can only be justified after monitoring complication rates after previous changes in bed rest protocols, as presented in this study.

Conclusions

Overall, an ilio-inguinal dissection is a demanding procedure requiring 'surgical skills' to reduce the overall complication rate, which is probably caused by impaired arterial blood supply through to thin skin flaps. In this study, older age, prolonged bed rest without Bohler Braun splint usage and higher BMI were independently associated with a complicated course following ilio-inguinal lymph node dissection for melanoma. Changing 'bed rest protocols' to 5 days without Bohler Braun splint usage, did not significantly increase the incidence of complications. The application of a short bed rest protocol could possibly increase cost-effectiveness of the ilio-inguinal lymph node dissection for melanoma.

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PART I

Predictive factors that enable patient selection for completion lymph node dissection

Chapter 3

Assessment of a new scoring system for predicting non-sentinel node positivity in sentinel node-positive melanoma patients

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ABSTRACT

Background. When completion lymph node dissection (CLND) is performed in sentinel node (SN)-positive melanoma patients, a positive non-sentinel node (NSN) is found in approximately 20% of them. Recently, Murali et al. proposed a new scoring system (non-sentinel node risk score, N-SNORE) to predict the risk of NSN positivity in SN-positive patients. The objectives of the current study were to identify factors predicting NSN positivity and to assess the validity of the N-SNORE in an independent patient cohort.

Methods. All SN-positive patients who underwent CLND at a single institution between 1995 and 2010 were analyzed. Characteristics of the patient, primary melanoma, and SN(s) were tested for association with NSN positivity. Missing values were reconstructed using multiple imputation to enable multivariable analysis.

Results. CLND revealed positive NSNs in 30 (23%) of 130 SN-positive patients. Primary melanoma regression (p=0.03) was independently associated with NSN positivity. After adjustment because of missing data on perinodal lymphatic invasion, N-SNORE proved to be a significant stratification model in our patient cohort (p=0.003): 5.9% NSN positivity in the very low risk category and 75.0% NSN positivity in the very high risk category.

Conclusions. Presence of regression in the primary melanoma was independently associated with a higher risk of NSN positivity. The slightly modified N-SNORE scoring system provided useful stratification of the risk for NSN positivity. However, lack of perinodal lymphatic invasion data may have reduced its predictive value.

Introduction

The incidence of melanoma is steadily increasing in the Western world. In the Netherlands its incidence has more than doubled in the past two decades, from 11.3 per 100,000 in 1989 to 26.3 per 100,000 in 2009.[1, 2] In the United States the incidence rate in 2007 was 18.7 per 100,000 and it is estimated that more than 70,000 people will be diagnosed with melanoma in 2012.[3, 4] Most melanoma patients in Western countries present initially with American Joint Committee on Cancer (AJCC) Stage I or II melanoma and 33-50% of these patients are diagnosed with Stage IA disease.[1, 5]

The most important predictors of outcome in melanoma patients with clinically localized disease are Breslow thickness, ulceration, and the mitotic rate of the primary tumor.[5, 6] The sentinel lymph node (SN) status, determined by sentinel lymph node biopsy (SLNB), is also of great importance for prognosis and in most studies this represents the strongest predictor of outcome.[7] Furthermore, patients undergoing SLNB, with completion lymph node dissection (CLND) if metastatic nodal disease is identified, seem to have better regional tumor control and survival according to the most recent interim analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I).[8]

Although CLND is usually performed in patients with a positive SN, one or more positive non-sentinel nodes (NSNs) are found in only 8-33 % of patients undergoing CLND.[7, 9, 10] In other words, approximately 4 out of every 5 SN-positive patients who receive a CLND will not have additional involved regional nodes identified. In theory, removal of uninvolved nodes will not improve the prognosis. As a result CLND, which is accompanied by considerable morbidity and costs, seems an unnecessary operation in approximately 80 % of SN-positive patients. Therefore, a tool for accurate preoperative prediction of NSN involvement is desirable, especially to identify a subgroup of patients with such low risk for NSN positivity that CLND can be safely avoided. Many studies have investigated clinical and histological factors that predict NSN positivity.[9-21] Recently, Murali et al. proposed a new scoring system for stratification of risk of NSN positivity which they termed the non-sentinel node risk score (N-SNORE).[21] The aims of the present study were to identify factors associated with NSN positivity in a cohort of Dutch patients and to independently assess the validity of the proposed N-SNORE.

Methods

All patients (n = 130) undergoing CLND after a positive SLNB at the Division of Surgical Oncology of the University Medical Center Groningen between 1995 and 2010 were included in this study.

To enable SLNB, lymphoscintigraphy with ^{99m}Tc nanocolloid was performed the day before surgery and patent blue was injected 15-20 minutes before the procedure. All basins identified by lymphoscintigraphy were explored surgically and all nodes that were hot and / or blue were removed.[22]

Histopathologic analysis of the SNs consisted of blocking in paraffin and cutting 4 µm thick sections at 4 different levels with 250 µm between each level. Sections at each level were stained with hematoxylin and eosin and immunohistochemically for S100 and Melan-A. If metastatic melanoma

was identified by histopathology or immunohistochemistry, the SLNB was considered positive and CLND was performed. For NSNs, histopathological analysis was performed on hematoxylin and eosin stained sections of cross-sectioned lymph nodes, and additional immunohistochemistry was not performed routinely.

Details of the patients, their primary tumors, SLNB, and CLND were prospectively collected in a database. The recorded parameters included: age, sex, histologic subtype of primary melanoma, Breslow thickness, Clark level of invasion, ulceration, mitotic rate, lymphovascular invasion, satellites, regression, number of harvested SNs, number and proportion of involved SNs, extranodal spread of tumor, maximum size of largest melanoma deposit in lymph node, and whether metastasis was detected by hematoxylin and eosin staining alone or by additional immunohistochemistry.

Statistics

Missing data were imputed (multiple imputation[23]) using a model with all factors. For the multiple imputation, we generated 5 iterations and combined the estimates and standard errors using Rubin's Rules (micombine in STATA). Prior to running the model we checked whether the data was missing at random. We used multiple imputation by chained equations which assumes a multivariate distribution exists without specifying its form. In STATA the ICE module was used to perform the multiple imputation. A model was built with all missing variables (as shown in Table 1) and outcome. Univariate and multivariable binary logistic regression analysis was used to identify independent predictors for NSN positivity. A full model including all variables that were deemed important for the outcome was built. Since Murali et al demonstrated a significant association with some of the variables, we included these variables in the model. A significance level of 5% was used to identify statistically significant results.

The N-SNORE as described by Murali et al. is a weighted score with a maximum sum of 11 points based on the following characteristics: sex (female=0, male=1), regression in primary melanoma (absent=0, present=2), proportion of harvested SNs containing metastatic melanoma (≤50%=0, >50%=2), perinodal lymphatic invasion in SN (absent=0, present=3), and maximum size of largest tumor deposit in the SN (≤0.5 mm=0, 0.51 to 2.00 mm=1, 2.01 to 10.00 mm=2, >10.00 mm=3). The authors created 5 risk groups based on the N-SNORE, which stratified the incidence of NSN positivity; very low (0%), low (5-10%), intermediate (15-20%), high (40-50%), and very high (70-80%). [21] Assessment of the proposed N-SNORE was done by chi-square testing. As the variable perinodal lymphatic invasion (3 of 11 points), defined as the presence of melanoma cells in lymphatic vascular channels in tissues beyond the capsule of the SN[24], was not recorded in the patients in the present study, the score was adjusted by rearranging the scores for the risk groups and subtracting 3 points from the total.

For the analyses STATA/SE 10.0 version was used (ICE, MIM, MICOMBINE and LOGISTIC).

Table 1. Clinicopathologic characteristics of 130 sentinel node positive patients and the association with non-sentinel node positivity

Characteristic		n (%)	%	MULTIPLE Imputation%	NSN positive (%)	p-value
Age (years)	<50	58	44.6	44.6	22.4	0.9
	≥50	72	55.4	55.4	23.6	
Sex	Female	55	42.3	42.3	20.0	0.5
	Male	75	57.7	57.7	25.3	
Histologic type	Superficial	75	57.7	58.1	24.3	**0.03**
	spreading	40	30.8	31.7	10.7	
	Nodular	4	3.1	4.8	41.9	
	Acral lentiginous	6	4.6	5.4	65.7	
	Other	5	3.8			
	Missing					
Breslow thickness (mm)	1.01-2.00	28	21.5	21.5	17.9	0.6
	2.01-4.00	70	53.9	53.9	22.9	
	>4.00	32	24.6	24.6	28.1	
Clark level	II / III	19	14.6	15.4	25.0	0.9
	IV / V	109	83.9	84.6	22.7	
	Missing	2	1.5			
Ulceration	No	72	55.4	56.3	23.8	0.8
	Yes	55	42.3	43.7	22.2	
	Missing	3	2.3			
Mitotic rate (no./mm2)	<5	55	42.3	51.5	24.2	0.8
	≥5	53	40.8	48.5	21.9	
	Missing	22	16.9			
Lymphovascular invasion	No	114	87.9	88.5	22.6	0.7
	Yes	15	11.5	11.5	26.7	
	Missing	1	0.8			
Satellites	No	118	90.7	91.5	23.5	0.7
	Yes	11	8.5	8.5	18.2	
	Missing	1	0.8			
Regression	No	64	49.2	72.3	18.5	**0.01**
	Yes	11	8.5	27.7	35.0	
	Missing	55	42.3			
Number of SN	1	34	26.2	26.2	20.6	0.4
	2	47	36.1	36.1	19.2	
	3 or more	49	37.7	37.7	28.6	
Number of positive SN	1	89	68.5	68.5	19.1	0.3
	2	33	25.4	25.4	30.3	
	3 or more	8	6.1	6.1	37.5	
Proportion involved	≤50%	60	46.2	46.2	20.0	0.4
	>50%	70	53.8	53.8	25.7	
Size of largest metastasis (mm)	≤0.50	35	26.9	28.0	13.7	**0.008**
	0.51-2.00	42	32.3	38.5	16.4	
	2.01-10.0	27	20.8	30.9	36.3	
	>10.0	3	2.3	2.6	64.7	
	Missing	23	17.7			
Extranodal growth	No	124	95.4	96.2	23.0	0.9
	Yes	4	3.1	3.8	24.0	
	Missing	2	1.5			
Detection H&E only	No	45	34.6	34.6	24.4	0.8
	Yes	85	65.4	65.4	22.4	

Abbreviations: SNs, sentinel nodes; H&E, hematoxylin and eosin.
P-values <0.05 printed in bold.
Median values and range of continuous variables: age 52.1 (20.5-81.0), Breslow 3.0 (1.1-13), mitotic rate 4 (0-20), number of SN 2 (1-3), number of positive SNs 2 (1-3), size of largest metastasis 1.3 (0-17).

Results

A total of 130 SN-positive patients [75 males (58%) and 55 females (42%): median age 51.5 (range 5 to 88) years] underwent CLND. The clinicopathologic characteristics of the patient cohort are presented in Table 1. The patients had one (68%) or more (32%) positive SNs. There were 57 axillary (44%), 55 groin (42%), 16 neck (12%), and 2 popliteal CLNDs. CLND was positive for metastatic melanoma in 30 patients (23%). Seventeen patients (57%) showed involvement of a single NSN, whereas 13 patients (43%) had more than one NSN involved (range 2 to 12).

Table 2. Univariate and multivariable logistic regression of factors predictive of non-sentinel node positivity

		Multivariable analysis		
Characteristic		**OR**	**95%CI**	**p-value**
Sex	Female	Reference		0.9
	Male	1.1	0.3-3.5	
Histologic type	Superficial spreading	Reference		0.1
	Nodular	0.6	0.2-2.4	
	Acral lentiginous	5.1	0.5-53.5	
	Other	4.9	0.6-41.3	
Breslow thickness	1.01-2.00	Reference		0.9
	2.01-4.00	0.9	0.3-3.5	
	>4.00	0.8	0.2-4.4	
Regression	No	Reference		**0.04**
	Yes	6.3	1.1-36.1	
Proportion involved	≤50%	Reference		0.6
	>50%	0.7	0.2-2.6	
Number of positive SN	1	Reference		0.6
	2	1.6	0.4-6.7	
	3 or more	2.3	0.3-20.0	
Size of metastasis	≤0.50	Reference		0.1
	0.51-2.00	0.9	0.2-3.8	
	2.01-10.0	3.5	0.7-16.4	
	>10.0	19.6	0.4-1044	

P-values <0.05 printed in bold.
Variables found to be associated with non-sentinel node positivity by Murali et al. were included in the multivariable model.

Factors associated with positive NSNs in CLND

Factors that were significantly associated with a positive NSN in univariate analysis were histologic subtype of the primary melanoma (p=0.03), the presence of regression (p=0.01), and larger size of the largest deposit in the SN (p=0.008) (Table 1). As shown in Table 2, presence of regression was associated with a positive NSN in multivariable logistic regression (OR 6.3; 95%CI 1.1-36.1; p=0.04). Other variables proposed in the N-SNORE were not associated with outcome in the multivariable analysis: sex (OR 1.1; 95%CI 0.3-3.5; p=0.9), the proportion of harvested SNs (OR 0.7; 95%CI 0.2-2.6;

p=0.6) and size of the metastasis (OR 0.9; 95%CI 0.2-3.8, 3.5; 95%CI 0.7-16.4, 19.6; 95%CI 0.4-1044 for 0.51-2.00, 2.01-10.0 and >10.0, respectively. Using bootstrap as standard error type, regression was not significantly associated with positive NSNs in the CLND (OR 6.3; 95%CI 0.9-44.4; p=0.06).

Table 3. Predictive value of original N-SNORE and modified N-SNORE

	N-SNORE - MIA * (Murali et al[20])				**Modified N-SNORE - UMCG ** (Present study)**			
Risk category	**Score**	Percentage of dataset (n=309)	Percentage NSN positive	**p**	**Score**	Percentage of dataset (n=130)	Percentage NSN positive	**p**
V ery low	**0**	2.6	**0**	**<0.001**	**0**	7.9	**5.9**	**0.003**
Low	**1 – 3**	40.7	**6.4**		**1 – 2**	25.5	**13.3**	
Intermediate	**4 – 5**	42.0	**16.3**		**3 – 4**	39.4	**21.1**	
High	**6 – 7**	11.7	**44.4**		**5 – 6**	23.5	**34.6**	
Very high	**≥8**	2.9	**77.8**		**7 – 8**	3.7	**75.0**	

* Melanoma Institute Australia.

** Dutch data University Medical Center Groningen: score adjusted after subtracting points for perinodal lymphatic invasion; max score 8 points.

N-SNORE components: sex (female=0, male=1), regression in primary melanoma (absent=0, present=2), proportion of harvested SNs containing metastatic melanoma (≤50%=0, >50%=2), perinodal lymphatic invasion in SN (absent=0, present=3), and maximum size of largest tumor in SN (≤0.5 mm=0, 0.51 to 2.00 mm=1, 2.01 to 10.00 mm=2, >10.00 mm=3); max score 11 points.

N-SNORE

In the present cohort, 7.8%, 46.6%, 35.9%, and 9.7% of patients were in the very low, low, intermediate, and high risk N-SNORE categories, respectively. No patients were classified in the very high risk category because no points were scored for perinodal lymphatic invasion. The NSN positivity rates for these risk groups were 5.9%, 19.8%, 24.5%, and 47.6%, respectively (p=0.04). When the N-SNORE system was adjusted for the lack of perinodal lymphatic invasion, there was better stratification of NSN positivity in our cohort (p=0.003), with 5.9% NSN positivity in the very low risk category and 75% NSN positivity in the very high risk category (Table 3). The measures of prediction accuracy showed a reasonable model fit (R2 0.21, linktest p=0.33 and percentage correctly classified 83.6%).

Discussion

Currently, CLND is recommended for all patients with a positive SN[25], although only around 20% of these patients will have metastatic melanoma in their NSNs. This retrospective study found that the previously proposed N-SNORE (after modification due to missing data on one parameter of N-SNORE, i.e. perinodal lymphatic invasion) was a statistically significant predictive model to stratify risk for NSN positivity.

Factors associated with NSN positivity

The rate of NSN positivity in this study was 23%, which is within the range of 8-33% reported in literature.[9, 10]

The most frequently cited factors associated with NSN positivity in the literature are thickness of primary tumor[9-11, 13-15, 18], size of largest SN metastasis[10, 11, 13-20], number of positive SN[12, 14, 18, 19], and perinodal lymphatic invasion[10, 16, 21]. In this study, we found size of largest metastasis in SLNB to be a predictor in univariate analysis (p=0.008). Histologic subtype of primary tumor was predictive of NSN positivity in univariate analysis (lower risk for nodular type), a factor that, to our knowledge, has not been described previously as a significant predictor of NSN positivity. Regression in the primary tumor was a predictor of NSN positivity in both univariate (p=0.01) and multivariable analysis (p=0.04). Previous studies that found regression to be a predictor of NSN positivity hypothesized that this could be due to an underestimate of primary tumor thickness and other features of aggressiveness (such as mitotic rate) in regressed melanoma.[10, 11, 21]

Notable factors that were not predictive in our study were Breslow thickness of the primary tumor and number of positive SNs. Furthermore, the proportion of affected nodes / total nodes in SLNB was not statistically significantly associated with NSN positivity, in contrast to the findings of Murali et al.[21]

N-SNORE

The N-SNORE model recently proposed by Murali et al. stratified risk for NSN positivity in a study of 309 SN-positive patients (p<0.001).[21] After modifying the score to correct for the missing variable perinodal lymphatic invasion in our dataset, we found a significant predictive value for the N-SNORE in our Dutch population of 130 SN-positive patients as well (p=0.003) (Table 3).

Comparison of the N-SNORE in both patient cohorts (Table 3) shows increasing NSN positivity rates over the increasing risk categories. The percentage of patients classified in the very low risk category was higher in the present study. However, the lower risk groups (very low and low) were associated with a higher rate of NSN positivity (5.9% and 13.3%, respectively). Therefore, in the study of Murali et al the N-SNORE provides better grounds for CLND omission. Addition of perinodal lymphatic invasion (if available) is likely to improve stratification of the N-SNORE, especially given the strength of the association of this parameter with NSN positivity in Murali et al's study. Therefore, the absence of perinodal lymphatic invasion data in our cohort prevents conclusive validation of the N-SNORE model.

Although a predictive score like the N-SNORE provides useful prognostic information for both physicians and patients, the use of a predictive score as an indicator for CLND avoidance should be validated before it can be recommended for routine clinical application. Moreover, the current second Multicenter Selective Lymphadenectomy Trial (MSLT-II) should demonstrate whether CLND following removal of a positive SN improves outcome compared to clinical and ultrasound monitoring of regional node fields with therapeutic lymph node dissection only in cases with manifest nodal metastasis.[26]

In conclusion, this retrospective study found regression in the primary melanoma to be an independent predictor of a higher risk for NSN positivity. Despite missing the variable perinodal lymphatic invasion, useful stratification of the risk of NSN positivity was achieved using the recently proposed N-SNORE. For final validation, the scoring system needs to be tested in other large, independent datasets, ideally containing details of perinodal lymphatic invasion.

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Chapter 4

Serum S-100B levels are associated with non-sentinel node positivity in 68 sentinel node-positive melanoma patients

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Submitted

ABSTRACT

Background. Completion lymph node dissection (CLND) in sentinel node (SN)-positive melanoma patients leads to substantial morbidity and costs, while only about 1 out of 5 patients have a metastasis in non-sentinel nodes (NSNs). The aim of the present study was to investigate if biomarkers Lactate Dehydrogenase (LDH) and S-100B in SN-positive patients are associated with NSN positivity and thus might identify patients in whom CLND could be omitted.

Methods. All SN-positive patients who underwent CLND at a single institution between 2004 and mid-2012 were analyzed. Serum LDH and S-100B values measured the day before CLND were tested for their association with NSN-positivity. Both the reference cutoff of our institution and an optimal cutoff determined by receiver operating characteristic analysis were tested for their association with NSN positivity.

Results. A positive NSN was found in 16 of the 68 patients (23.5%) undergoing CLND. Univariate analysis revealed Breslow thickness (p=0.04), number of positive SNs (p=0.02), proportion of involved SNs (p=0.04), size of largest metastasis in SLNB (p=0.009), and S-100B value (p=0.001) to be associated with NSN positivity. LDH level was not significantly associated with NSN positivity (p=0.11). S-100B with an obtained optimal cutoff of 0.07 µg/l was a significant independent predictor for NSN positivity in multivariable analysis (OR 8.88; p=0.006).

Conclusions. The results of this study show that S-100B with a cutoff within the reference interval could improve NSN risk scores to select SN positive patients in whom CLND could safely be omitted in the future.

Introduction

The most important predictors of prognosis in melanoma patients are tumor thickness according to Breslow, presence of ulceration, and mitotic rate of the primary tumor.[1, 2] In addition to these primary melanoma characteristics, the sentinel node (SN) status determined by sentinel lymph node biopsy (SLNB) is of great importance for prognosis.[3] SLNB is therefore recommended by the American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline, especially in intermediate-thickness melanomas (1-4 mm Breslow thickness).[4] The fourth interim analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT I) reveals that SLNB followed by immediate completion lymph node dissection (CLND) for occult nodal metastasis might lead to improved melanoma specific survival.[5, 6]

Generally, when CLND follows a positive SN, one or more positive non-sentinel nodes (NSNs) are found in 8-33% of patients.[3, 7, 8] In other words, roughly about 4 out of 5 patients will not have affected regional nodes, apart from the positive SN. This subgroup of SN-positive patients will not improve their outcome through CLND. For these patients a CLND, causing morbidity (wound infections, lymph edema, and impaired function) and economic burden, should be avoided.[9, 10] The possibility of selecting a subgroup of patients with a low risk for NSN positivity could be a key element for omitting an unnecessary CLND safely.

Various parameters have been investigated to select patients who could be treated safely without performing a CLND. Association of clinicopathologic factors with NSN positivity, like Breslow thickness[7, 8], maximum size of metastasis in SN[8, 11-14], number of positive nodes in SLNB[11], and perinodal lymphatic invasion[8, 13] have been described in literature. However, those parameters lack predictive strength to stratify risk for NSN positivity and so risk scores combining these parameters are suggested[7, 13].
The predictive value of biomarkers has not been investigated for the selection of SN-positive patients in whom CLND could be omitted. Serum biomarkers could be stronger predictors of NSN positivity or complement suggested risk scores.

For melanoma, two biomarkers have been extensively studied: Lactate Dehydrogenase (LDH) and S-100B.[15] The melanoma associated molecule S-100B was found to be a tumor marker in stage III and IV disease.[16, 17] Elevated levels of serum S-100B were found to be associated with increased risk for recurrence and decreased survival in melanoma patients presenting with palpable nodal metastases.[18]
The aim of the present study was to investigate if serum levels of LDH and S-100B in SN-positive patients could be associated with NSN positivity and thus might identify patients in whom CLND could safely be omitted.

Methods

From 2004 to mid-2012, all cutaneous melanoma patients with tumor-positive sentinel lymph nodes eligible for CLND were prospectively entered in this study. Sentinel lymph node biopsy was only performed in patients presenting with a primary melanoma >1 mm Breslow thickness (except for one patient who had opted for SLNB with a melanoma of 0.8 mm thickness, presence of ulceration, and mitotic rate >1 mm^2) without clinically manifest lymph node metastases.

The study cohort consisted of patients who earlier underwent wide local excision and SLNB at the University Medical Center Groningen (UMCG, a tertiary referral center for melanoma patients) as well as patients who were referred to this institution. In case of referral, histopathologic revision of the primary tumor and the harvested sentinel lymph nodes was performed at the UMCG before scheduling CLND.

Histopathologic processing of the SNs consisted of blocking in paraffin and cutting of 4 µm sections at 4 different levels for routine hematoxylin and eosin staining with additional immunohistochemistry for S-100B and Melan-A. If metastatic melanoma was found during this procedure the SLNB was considered positive and CLND was performed. For NSNs, histopathologic analysis was done by cross-section of each lymph node with subsequent hematoxylin and eosin staining without additional immunohistochemistry.

Characteristics of the patients, the primary tumors, SLNB, and CLND were collected in a database. The recorded parameters included: age, sex, histologic type, tumor thickness according to Breslow, Clark level, ulceration, mitotic rate, lymphovascular invasion, regression, total number of harvested SNs, number of involved SNs, proportion involved SN, size of the largest metastasis in SN, extranodal growth pattern, and whether metastasis was detected by hematoxylin and eosin staining alone or by additional immunohistochemistry. LDH and S-100B values were measured the day prior to CLND.

Tumor marker assay and reference cutoff

LDH was analyzed routinely by means of Roche Modular (Hitachi) with an enzymatic activity measurement; normal values of LDH were considered to be below the reference cutoff of 250 U/l.

S-100B levels were calculated on the basis of a calibration curve and checked against internal standards with a known concentration of S-100B. The reference values for the S-100B assay (Liaison Sangtec 100) were established by analysis of S-100B values of 120 healthy individuals according to the CLSI C28-A2 guideline[19], resulting in a reference cutoff point of 0.15 µg/l at our institution.

Statistical analysis

Characteristics of the patient (age and sex), primary melanoma (histologic type, Breslow thickness, Clark level, ulceration, mitotic rate, lymphovascular invasion, and regression), and harvested SNs (total number of nodes, number of involved nodes, proportion involved SN, size of the largest nodal metastasis, extranodal growth pattern, and detection by hematoxylin and eosin staining only) were analyzed for their association with NSN positivity using Fischer's exact test or the Chi squared test for categorical variables and the Mann-Whitney U test for continuous variables.

First, the association of continuous data on LDH and S-100B with NSN positivity was studied using the Mann-Whitney U test. When $p<0.05$ for the continuous data, association with NSN positivity was tested for the reference cutoff (based on the reference group) and an 'optimal cutoff point' determined by a receiver operating characteristic (ROC) curve. The optimal cutoff was defined as the value showing the highest sum of sensitivity and specificity in the ROC curve. All characteristics associated with NSN positivity on a 10% significance level were entered in a multivariable model. Subsequently, logistic regression analysis was performed, using a p-value <0.05 to identify significant independent predictors. Both continuous and quantitative discrete characteristics were treated as quantitative variables in both univariate and multivariable analyses, except for LDH and S-100B levels which were categorized for multivariable analysis. Finally, Mann-Whitney U test and Kruskal-Wallis test were used to compare serum S-100B levels in the melanoma patients with S-100B levels in 120 healthy individuals who responded to leaflets in our hospital asking for volunteers. The serum of these volunteers was also used to determine the reference cutoff point.

Results

A total of 68 SN-positive patients, consisting of 29 females (42.6%) and 39 males (57.4) with a median age of 53 (range 24-89) years, were studied. In 18 of these patients (26.5%) more than one SN contained a micrometastasis.

Positive NSNs were found in 16 of the 68 patients (23.5%) undergoing CLND. Of these 16 patients, 6 (37.5%) showed involvement of a single NSN, whereas 10 patients (62.5%) had more than one NSN involved. Fifty-two patients (76.5%) had no metastases found in the NSNs.

Factors associated with positive NSNs in CLND

Univariate analysis revealed the following characteristics to be associated with NSN positivity: Breslow thickness ($p=0.04$), number of positive SNs ($p=0.02$), proportion of involved SNs ($p=0.04$), and size of largest metastasis in SLNB ($p=0.009$). S-100B analyzed as continuous variable was associated with NSN positivity ($p=0.001$). LDH as continuous variable did not show a significant association with NSN positivity in univariate analysis ($p=0.11$) and was therefore not further analyzed. (Table 1)

Association of S-100B with NSN positivity using the reference cutoff

According to the reference cutoff 0.15 µg/l, serum S-100B values were elevated in 5 patients (7.4%). This cutoff showed low sensitivity of 31% and high specificity of 100% for NSN positivity (all patients with S-100B above cutoff point were NSN positive). In univariate analysis the reference cutoff showed significant association with NSN positivity (p=0.001). The percentage of NSN positivity in patients with marker values below this cutoff point was 17.5% (false negative rate 69%). (Table 1)

Association of S-100B with NSN positivity using the optimal cutoff

ROC curve analysis of preoperative S-100B values predicting NSN positivity showed an area under the curve of 0.77 (Figure 1). S-100B had an optimal cutoff point of 0.07 µg/l. The obtained optimal S-100B cutoff showed a more useful association with NSN positivity (sensitivity 75%, specificity 77%; p<0.001) than the reference cutoff point (sensitivity 31%, specificity 100%; p=0.001). In multivariable analysis, S-100B with the optimal cutoff was a significant independent predictor for NSN positivity (OR 8.88; p=0.006). The percentage of NSN positivity in patients with marker values below the cutoff point was 9.1% for the optimal S-100B cutoff (false negative rate 25%). (Table 1)

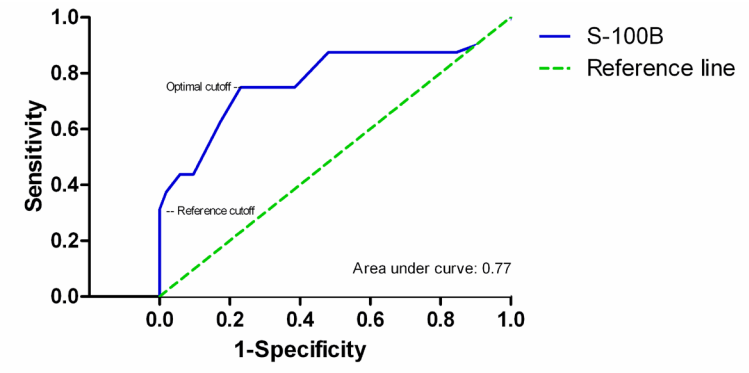

Figure 1. ROC curve of S-100B predicting NSN status

Table 1. Univariate and multivariable analysis of preoperative characteristics of 68 SN-positive patients undergoing CLND tested for their association with NSN positivity

Characteristic	n	(%)	NSN positivity (%)		p	Multivariable OR (95% CI)	p
Age (years)							
Continuous (median, range)	53	24-89			0.20		
<50	*31*	*(45.6)*	*5/31*	*(16.1)*			
≥50	*37*	*(54.4)*	*11/37*	*(29.7)*			
Sex							
Female	29	(42.6)	5/29	(17.2)	0.29		
Male	39	(57.4)	11/39	(28.2)			
Histologic type							
Superficial spreading	46	(67.6)	9/46	(19.6)	0.25		
Nodular	16	(23.5)	4/16	(25.0)			
Acral lentiginous	2	(2.9)	1/2	(50.0)			
Other	4	(5.9)	2/4	(50.0)			
Breslow thickness (mm)							
Continuous (median, range)	2.9	0.8-11.0			**0.04**	1.04 (0.71-1.52)	0.86
T2: 1.01-2.00	*20*	*(29.4)*	*3/20*	*(15.0)*			
T3: 2.01-4.00	*28*	*(41.2)*	*6/28*	*(21.4)*			
T4: >4.00	*20*	*(29.4)*	*7/20*	*(35.0)*			
Clark level							
II/III	12	(17.6)	2/12	(16.7)	0.86		
IV	38	(55.9)	9/38	(23.7)			
V	18	(26.5)	5/18	(27.8)			
Ulceration							
No	37	(54.4)	7/37	(18.9)	0.33		
Yes	31	(45.6)	9/31	(29.0)			
Mitotic rate							
Continuous (median, range)	5	1-23			0.78		
<5	*31*	*(49.2)*	*6/31*	*(19.4)*			
≥5	*32*	*(50.8)*	*8/32*	*(25.0)*			
Unknown	*5*						
Lymphovascular invasion							
No	62	(91.2)	13/62	(21.0)	0.14		
Yes	6	(8.8)	3/6	(50.0)			
Regression							
No	59	(88.1)	15/59	(25.4)	0.67		
Yes	8	(11.9)	1/8	(12.5)			
Unknown	*1*						
Number of SN							
Quantitative (median, range)	2	1-6			0.51		
1	*19*	*(27.9)*	*5/19*	*(26.3)*			
2	*22*	*(32.4)*	*6/22*	*(27.3)*			
3 or more	*27*	*(37.9)*	*5/27*	*(18.5)*			
Number of positive SN							
Quantitative (median, range)	1	1-4			**0.02**	1.24 (0.45-3.42)	0.68
1	*50*	*(73.5)*	*8/50*	*(16.0)*			
2	*13*	*(19.1)*	*6/13*	*(46.2)*			
3 or more	*5*	*(7.4)*	*2/5*	*(40.0)*			

Table 1 *Continued. Univariate and multivariable analysis of preoperative characteristics of 68 SN-positive patients undergoing CLND tested for their association with NSN positivity*

Characteristic	n	(%)	NSN positivity	(%)	p	Multivariable OR (95% CI)	p
Size of metastasis (mm)							
Continuous (median, range)	1.5	0.01-17.0			**0.009**	1.09 (0.92-1.30)	0.32
≤0.50	*15*	*(25.4)*	*0/15*	*(0)*			
0.51-2.00	*20*	*(33.9)*	*4/20*	*(20.0)*			
2.01-10.0	*18*	*(30.5)*	*6/18*	*(33.3)*			
>10.0	*6*	*(10.2)*	*2/6*	*(50.0)*			
unknown	*9*						
Extranodal growth							
No	66	(97.1)	15/66	(22.7)	0.42		
Yes	2	(2.9)	1/2	(50.0)			
Detection H&E only							
No	18	(26.5)	4/18	(22.2)	0.88		
Yes	50	(73.5)	12/50	(24.0)			
Preoperative LDH (U/l)							
Continuous (median, range)	178	110-389			0.11		
LDH Reference cutoff							
≤250	64	(94.1)	14/64	(21.9)	0.23		
>250	4	(5.9)	2/4	(50.0)			
Preoperative S-100B (µg/l)							
Continuous (median, range)	0.06	0.02-1.65			**0.001**		
S-100B Reference cutoff							
≤0.15	63	(92.6)	11/63	(17.5)	**0.001**	N/A**	
>0.15	5	(7.4)	5/5	(100)			
S-100B Optimal cutoff *							
≤0.07	44	(64.7)	4/44	(9.1)	**<0.001**	1	**0.006**
>0.07	24	(35.3)	12/24	(50.0)		8.88 (1.90-41.7)	

Continuous characteristics were tested using Mann-Whitney U test, quantitative discrete characteristics were tested using logistic regression analysis. Categorical characteristics were tested with Chi squared test.
Entered in multivariable mode: Breslow thickness, number of positive SN, size of largest SN metastasis, S-100B optimal cutoff.
All p-values <0.05 are printed in bold.
***** Optimal S-100B cutoff based on receiver operating characteristic curve.
** N/A: not addressed due to 100% NSN positivity for S-100B levels >0.15 µg/l.
Abbreviations: SN, sentinel node; NSN, non-sentinel node; CLND, completion lymph node dissection; H&E, hematoxylin and eosin.

S-100B levels in SN-positive melanoma patients compared to healthy individuals

The serum S-100B levels measured in 120 healthy individuals (median 0.07; range 0.01-0.59) did not significantly differ from the serum levels in 68 SN-positive patients (median 0.06; range 0.02-1.65; p=0.44) (Figure 2). When the melanoma patients were categorized into a NSN negative and a NSN positive group significant differences in S-100B levels were found. For 120 healthy individuals, 52 NSN negative melanoma patients, and 16 positive melanoma patients, the median S-100B levels were 0.07 (range 0.01-0.59), 0.05 (range 0.02-0.14), and 0.09 (range 0.02-1.65), respectively (p=0.001). NSN negative patients showed lower S-100B levels (p=0.03), and NSN positive patients show higher levels compared to healthy individuals (p=0.008). (Figure 3)

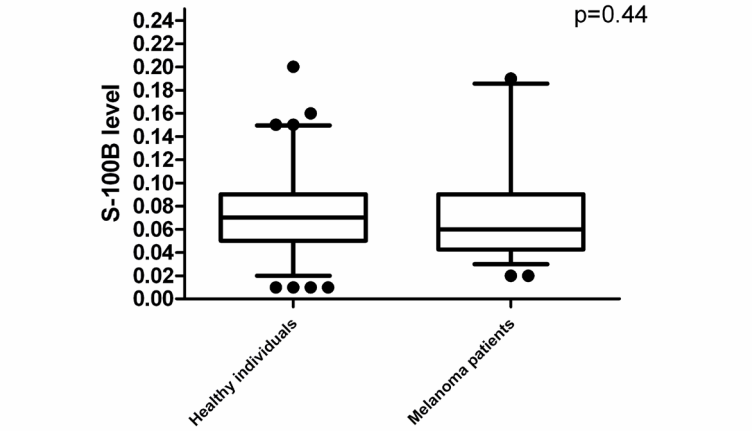

Figure 2. Comparison of S-100B levels in healthy individuals and SN positive melanoma patients

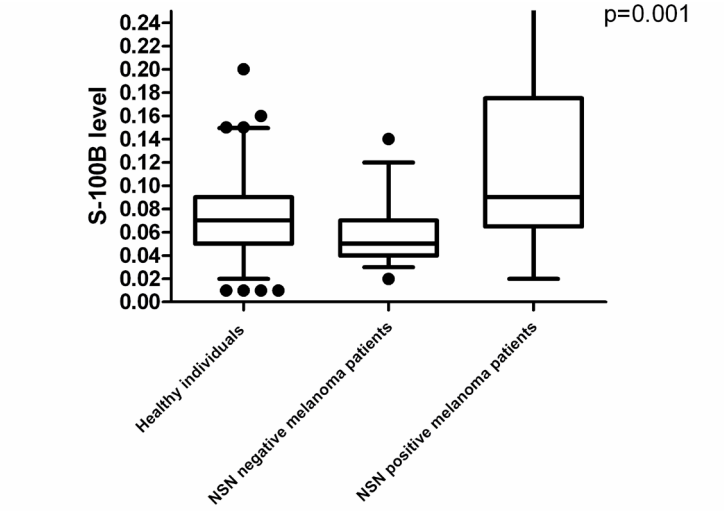

Figure 3. Comparison of S-100B levels in healthy individuals and SN positive melanoma patients according to NSN status

Discussion

Based on a systematic review, the American Society of Clinical Oncology and the Society of Surgical Oncology recently officially stressed the importance of SLNB performance for accurate melanoma staging, especially for intermediate-thickness melanomas (1-4 mm Breslow thickness). In case of a positive SN, performance of CLND is recommended in their guideline until the risks of CLND omission are fully explored by the pending second Multicenter Selective Lymphadenectomy Trial (MSLT-II).[4, 20].

In anticipation of MSLT-II results, various studies were performed to identify clinicopathologic factors that predict of risk for NSN positivity to enable future patient selection for CLND omission. In particular, the size of the sentinel node metastasis seemed a good predictor for this purpose. Especially the investigators of the Daniel den Hoed Cancer Center in Rotterdam have performed extensive research on this and developed the so called 'Rotterdam Criteria' for SN tumor load. In their studies, a SN metastasis smaller than 0.1 mm showed to be predictive for low NSN positivity risk and was even suggested to be considered SN negative[11, 21] Although the impact on prognosis of CLND omission in patients with minimal SN tumor burden is currently being explored by the EORTC MINITUB registration study[22], more recently discussion about its value rose because underestimation of the deposit size could possibly prevent safe use of this factor for CLND avoidance.[14, 23]. While this debate triggers further investigation on histopathologic predictors of NSN positivity, no studies concerning the use of biomarkers to improve patient selection for CLND avoidance are being published.

This study is, to our knowledge, the first to investigate the association of LDH and S-100B levels with NSN positivity in SN-positive melanoma patients. For AJCC stage I and II, various studies have concluded that neither serum S-100B nor LDH were capable of predicting the SN status because of low sensitivity of these markers with the used cutoff points.[24-26] However, all these studies only used cutoff points based on a group of apparently healthy individuals.

Of the 68 SN-positive melanoma patients who underwent CLND, 16 patients (23.5%) showed metastatic involvement of NSNs. Using the serum marker S-100B with a cutoff below the 0.15 µg/l reference cutoff of our institution enabled useful stratification of risk for NSN positivity. The cutoff of 0.07 µg/l, obtained by ROC analysis, was an independent predictor for NSN positivity (OR 8.88; p=0.006). The S-100B marker showed a 9.1% NSN positivity in patients with values below the 0.07 µg/l cutoff versus 50.0% for patients with values above this cutoff. S-100B using the standard 0.15 µg/l reference cutoff, although significantly associated, was not useful to stratify risk for NSN positivity due to low sensitivity. Moreover, LDH as continuous variable was not associated with NSN positivity.

Other variables associated with NSN positivity in univariate analysis were Breslow thickness, number of positive nodes in SLNB, and size of largest metastasis in SN. Although not significant on multivariable analysis, these three factors reflect the most reported predictors for NSN positivity in current literature.[7, 8, 11-13, 21, 27-34] These histopathologic parameters, especially when combined with clinical parameters in a NSN risk score, were previously found to enable stratification of risk for NSN positivity.[7, 13]

In current clinical practice, S-100B levels above the reference cutoff (0.15 µg/l in our institution) are used as an indicator for tumor load in stage III and IV melanoma.[16-18] Predicting NSN positivity with the reference cutoff of 0.15 µg/l however resulted in a low sensitivity. This was significantly improved when using the cutoff of 0.07 µg/l, making S-100B a useful predictor for NSN positivity. A predictive capacity for S-100B with a cutoff point within the reference interval might feel counterintuitive, as S-100B values within the reference range of healthy individuals could hardly reflect melanoma tumor load. However, biochemical studies show that the S-100B protein inhibits tumor suppression by p53 and apoptosis in melanoma, thereby probably contributing to disease progression.[35, 36] Following this theory, it could be hypothesized that with increasing inherent S-100B levels metastatic tendency of melanoma cells enhances, increasing the risk for NSN positivity. In this situation, patients with higher, although within the 'normal' range, serum S-100B originating from e.g. the neurological system would show more aggressive melanoma tumor biology and higher risk for NSN involvement. This mechanism, with the S-100B protein as driver rather than passive marker, might explain the finding of a useful predictive cutoff below the reference cutoff of 0.15 µg/l in the present study.

Comparison of S-100B levels in healthy individuals and melanoma patients in the present study seem to support the latter theory. Serum S-100B levels in healthy individuals and SN-positive melanoma patients were found to be similar (Figure 2). When categorized for NSN status, NSN negative patients showed lower S-100B levels (p=0.03), and NSN positive patients show higher levels compared to healthy individuals (p=0.008) (Figure 3).

Compared to other described predictors of NSN positivity, S-100B with cutoff 0.07 µg/l showed a high OR and relative good sensitivity (univariate OR 8.88; sensitivity 75%).[7, 8, 11-13]. To enable clinical applicability, the accurateness of NSN positivity risk stratification should be further increased by combining the S-100B value with other clinicopathologic predictors in a risk score.

Prediction of NSN positivity by integrating the preoperative S-100B level into a NSN risk score could prevent the performance of unnecessary CLND, entailing costs and a high risk for complications, in a substantial number of patients. In this study, selection using the cutoff level of 0.07 µg/l would mark 64.7% of patients as low risk based on S-100B level alone (Table 1), although combining S-100B with other predictors will lower this percentage.

Before using the biomarker S-100B for omitting CLND, its predictive capacity and sensitivity should be validated in large independent patient cohorts. Moreover, the current MSLT-II trial should first demonstrate whether CLND following removal of a positive SN improves outcome compared to clinical and ultrasound monitoring of regional node fields with therapeutic lymph node dissection only in cases with manifest nodal metastasis.[20]

In summary, this study with a limited number of patients shows that S-100B levels of SN-positive melanoma patients are independently associated with NSN positivity. Using a S-100B cutoff point within the reference interval could further improve selection of SN positive patients in whom CLND could safely be omitted by integration of this biomarker in NSN risk scores. However, the findings of the present study need to be verified in a large independent cohort of SN-positive patients.

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PART II

Melanoma follow-up and prognostic factors in surgery for nodal recurrences

Chapter 5

Cutaneous melanoma: medical specialists' opinions on follow-up and sentinel lymph node biopsy

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Submitted

ABSTRACT

Background. The purpose, frequency and content of follow-up (FU) visits have been widely debated for all common malignancies, including melanoma. The aim of this study was to gain insight into Dutch medical specialists' opinions on melanoma FU and to assess their views on sentinel lymph node biopsy (SLNB).

Methods. All members of the Dutch Society of Surgical Oncology and the Dutch Society of Dermatology and Venereology were invited to complete a web-based questionnaire, consisting of 25 questions addressing the following topics: 1) respondent characteristics, 2) knowledge of national melanoma guideline, 3) opinions on melanoma FU, and 4) view on the significance of SLNB.

Results. A total of 378 respondents (response=37%) started the survey, including 173 surgeons (46%) and 205 dermatologists (54%). With the exception of one, respondents (99.7%) reported that they knew the content of the Dutch national melanoma guideline. Of these, 97% agreed that the purpose of FU was detection of local recurrence and 92% agreed that it was detection of a second primary. Concerning frequency of FU in the first 10 years after diagnosis, 42% preferred a less frequent FU than indicated by the current guideline, while 4% preferred more frequent FU. Dermatologist and surgeon should be involved in FU according to 77% and 37% of respondents, respectively.

Conclusion. The majority of Dutch medical specialists consider melanoma FU to be primarily an instrument to detect recurrences and secondary primaries. The frequency of FU, as prescribed by the current guideline, could be reduced according to 42% of respondents.

Introduction

As the number of patients with cancer continues to increase, medical specialists are striving to optimize treatment and follow-up (FU). Among various types of cancer, melanoma has one of the fastest increasing incidence rates in the western world. In the Netherlands the incidence of melanoma doubled in the past two decades, from 11.3 per 100 000 in 1989 to 26.3 per 100 000 in 2009.[1] In the United States, it is estimated that over 70 000 people will be diagnosed with melanoma in 2012.[2]

The purpose, frequency, and content of follow-up visits have been widely debated for all common malignancies, including melanoma. To date, high frequency FU, including up to four hospital visits per year, is recommended by national guidelines in countries with the highest melanoma incidence.[3] While medical specialists' opinions on the purpose and effectiveness of FU have been investigated for other malignancies, such as colon and breast cancer[4, 5], views on FU for melanoma remain unknown.

The aim of this study was to examine Dutch medical specialists' knowledge of the national melanoma guideline and to gain insight into their opinions on the purpose, frequency, and organization of FU in melanoma patients through a web-based survey. Additionally, respondents' views on sentinel lymph node biopsy (SLNB) were assessed.

Methods

Procedure and respondents

An e-mail explaining the goal of the study, an invitation to participate, and a hyperlink to the questionnaire was sent by the investigators to all members of the Dutch Society of Surgical Oncology (n=435 surgeons) and the Dutch Society of Dermatology and Venereology (n=600 dermatologists) in May 2010. A reminder email was sent after four weeks. All completed questionnaires were processed anonymously.

Instrument

A 25-question, web-based questionnaire was created using www.surveymonkey.com. In the present article we address the questions dealing with the following four subjects: 1) characteristics of respondent (five questions), 2) knowledge and adherence to the current Dutch melanoma guideline (three questions), 3) opinions on FU, including purpose, frequency and duration, and organization (seven questions, with accompanying subquestions), and 4) respondents' opinions on the guideline's recommendations for SLNB (three questions).

Questions on subjects one through three were derived from the questionnaire on medical specialists' attitude on FU in breast cancer patients from van Hezewijk et al. and modified to fit incidence and disease characteristics of malignant cutaneous melanoma.[4]

Current national guideline

The current Dutch melanoma skin cancer guideline, published in 2005, recommends a single FU visit for melanomas thinner than 1 mm according to Breslow.[6] For melanomas between 1 mm and 2 mm, the FU schedule after diagnosis consist of four visits during the first year, three visits during the second year, and two visits per annum up to the fifth year. Patients with a melanoma thicker than 2 mm are additionally evaluated annually during years 6 to 10 after diagnosis.

Regarding the SLNB, the 2005 Dutch melanoma guideline states that this procedure is not part of standard diagnostics of cutaneous melanoma and that the procedure has to be reserved for patients who want to be optimally informed about stage of their disease.

Statistical analysis

Frequencies and percentages were calculated. Differences between specialists with a surgical and a dermatological background were analyzed using chi-square tests with a significance level of 5%. Figures were created using GraphPad Prism 5.00. Statistical analysis was performed using the SPSS software package (SPSS 18.0, Chicago, Illinois, USA).

Results

Respondents' characteristics

A total of 378 respondents (response rate = 37%) started the survey, including 173 surgical (46%) and 205 dermatological (54%) medical specialists (Table 1). Of these, 352 respondents (93%) completed the questionnaire. Table 1 shows that respondents were from all types of hospitals with almost half working in a district training hospital. Twenty-eight percent of respondents (39% of surgeons and 19% of dermatologists, $p<0.001$) indicated that fewer than 30 new melanoma patients were diagnosed and treated in their hospital annually. Eighty-nine percent of medical specialists themselves (88% of surgeons and 90% of dermatologists, $p=0.559$) treated fewer than 30 new melanoma patients annually.

Current guideline

All but one of the medical specialists (99.7%) indicated they knew the content of the national melanoma skin cancer guideline. Of these, 36% responded they always followed the guideline's recommendations while 64% stated they incidentally deviated from it for an appropriate reason (percentages similar for surgeons and dermatologists). Forty-two percent reported that the national guideline was integrated into local hospital guidelines. The remaining 58% indicated that the national guideline was not integrated into a local guideline (no difference between surgeons and dermatologist, $p=0.374$).

Table 1. Characteristics of 378 respondents

Characteristic	n	%
Discipline		
Surgical oncologist	124	32.8
Surgeon	33	8.7
Surgical resident	16	4.2
Dermatologist	175	46.3
Dermatological resident	30	7.9
Type Hospital		
University Hospital	84	22.2
District training hospital	173	45.8
District non-training hospital	106	28.0
Private clinic	15	4.0
New patients per year in hospital		
0-10	14	3.7
11-20	39	10.3
21-30	52	13.8
31-40	45	11.9
41-50	39	10.3
>50	123	32.5
Unknown	66	17.5
New patients per year for specialist		
0-10	125	33.1
11-20	161	42.6
21-30	50	13.2
31-40	17	4.5
41-50	9	2.4
>50	7	1.9
Unknown	9	2.4
Follow-up contacts per week for specialist		
<1	119	31.5
1-2	143	37.8
3-5	85	22.5
6-10	21	5.6
>10	10	2.6

Follow-up

- *Purpose and goals*

Ninety-seven percent of respondents (totally) agreed that detection of local recurrences was a goal of FU. Percentages of specialists (totally) agreeing on other purposes of FU were: 92% on detection of a second primary, 84% on detection of regional or distant metastases, 72% on detection of late effects of treatment, and 65% on identifying psychological problems. Fewer than half of respondents (totally) agreed that assessing quality of life and recording patient status for research purposes were a purpose of FU (48% and 22%, respectively). (Figure 1a)

Opinions on the purpose of FU differed significantly between surgeons and dermatologists on three items. The percentage of surgeons (totally) agreeing that detection of second primaries and detection of regional and distant metastasis were a purpose of FU was lower than that of dermatologists: 84% versus 97% ($p<0.001$) and 74% versus 93% ($p<0.001$), respectively. Fewer dermatologists (totally) agreed that research was a purpose of FU than surgeons (18% versus 40%, $p<0.001$). (Figure 1b)

Sixty-six percent of specialists (55% of surgeons and 78% of dermatologists, $p<0.001$) (totally) agreed that early detection of a local recurrence or secondary primary would improve the chance for cure. Twenty-four percent thought that a more frequent FU would improve quality of life (14% of surgeons and 32% of dermatologists, $p<0.001$).

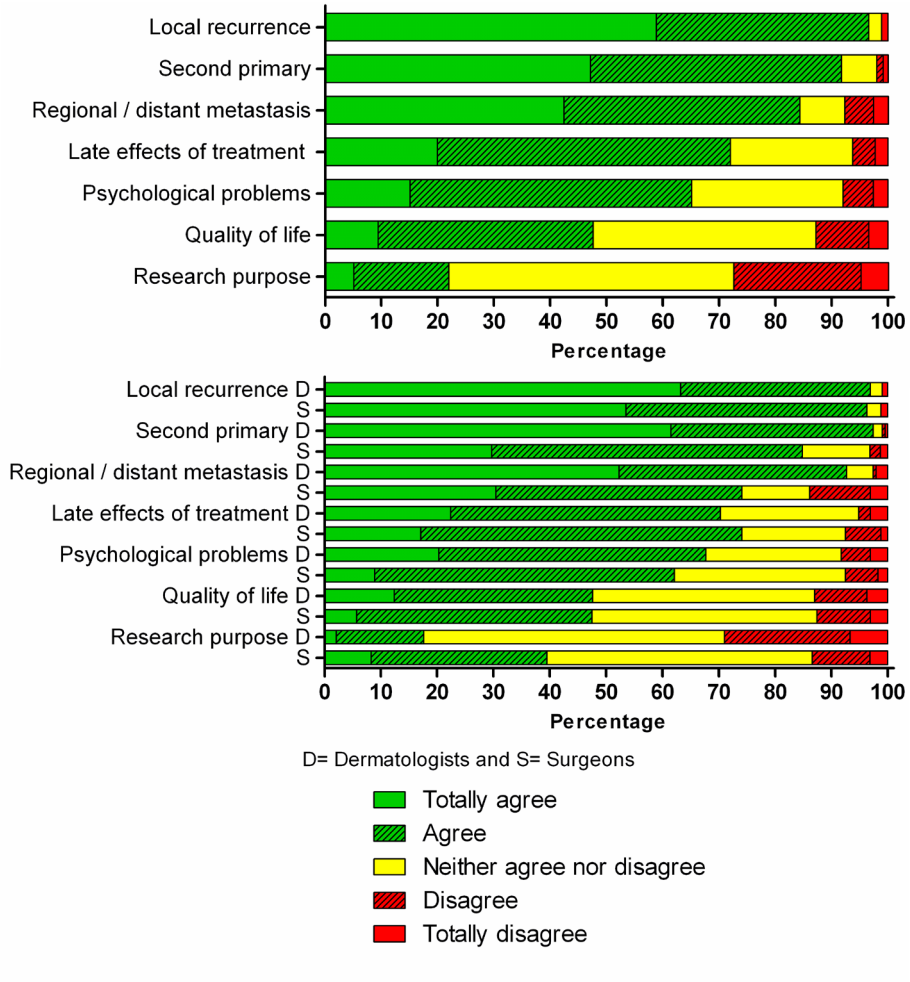

Figure 1. (a) Purpose of follow-up; (b) Purpose of follow-up according to Dermatologists and Surgeons

- *Frequency of visits*

The current national guideline prescribes a single FU visit after curative treatment of a primary melanoma thinner than 1 mm according to Breslow. Of all respondents, 27% totally agreed, 54% partially agreed, and 19% disagreed. Ten percent of surgeons disagreed while 38% totally agreed, and 27% of dermatologists disagreed while 18% totally agreed ($p<0.001$). When asked what the optimal FU frequency would be according to melanoma stage, compared to the current guideline recommendations, a slightly different pattern for stage Ia melanoma emerged: 52% of specialists answered they considered a single FU consultation for stage Ia disease to be good, 39% of specialists would prefer a more frequent FU schedule, and 4% would prefer less frequent FU (Figure 2a). For the more advanced stages of melanoma, only between 1% and 4% of the respondents would prefer more frequent FU. Less frequent FU was preferred by 45% of respondents for stage Ib disease, by 37% for stage IIa disease, by 32% for stage IIb, by 29% for IIc, and by 22% for stage III disease. (Figure 2a) Generally over the first 10 years after diagnosis, a less frequent FU was preferred by 42% of respondents and only 4% indicated they would like more frequent FU. Six percent of respondents indicated they would like FU visits to continue beyond the tenth year after diagnosis. (Figure 2b)

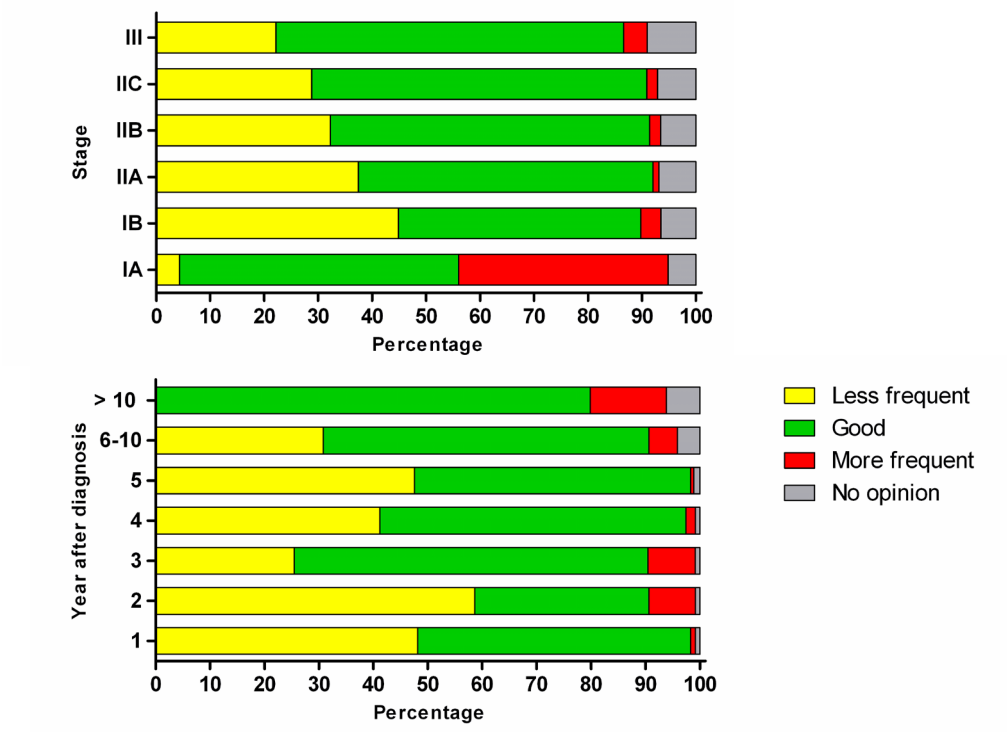

Figure 2. (a) Preferred follow-up frequency according to melanoma stage; (b) Preferred follow-up frequency according to year after diagnosis

- *Responsibility*

When asked which professionals currently perform FU after primary treatment, 56% of the respondents (63% of surgeons and 50% of dermatologists) answered a dermatologist as well as a surgeon, 30% (9% of surgeons and 47% of dermatologists) answered the dermatologist only, and 14% (26% of surgeons and 3% of dermatologists, p<0.001) stated the surgeon only. Five percent stated that a physician assistant or nurse practitioner was involved. When asked which professional should always, never, or in select cases be involved in the FU of melanoma, 77% (59% of surgeons and 91% of dermatologists, p<0.001) answered a dermatologist should always be involved and 37% (50% of surgeons and 25% of dermatologists, p<0.001) replied a surgeon should always be involved. Of the respondents, 21% (34% of surgeons and 10% of dermatologists, p<0.001) indicated a physician assistant or nurse practitioner should always be involved in FU and 5% (6% of surgeons and 3% of dermatologists, p=0.067) responded that a general practitioner (GP) should always be involved. In contrast, respondents stated some specialists should never be involved in melanoma FU: 43% excluded the GP, 26% the physician assistant or nurse practitioner, 2% the surgeon, and 2% the dermatologist. (Figure 3)

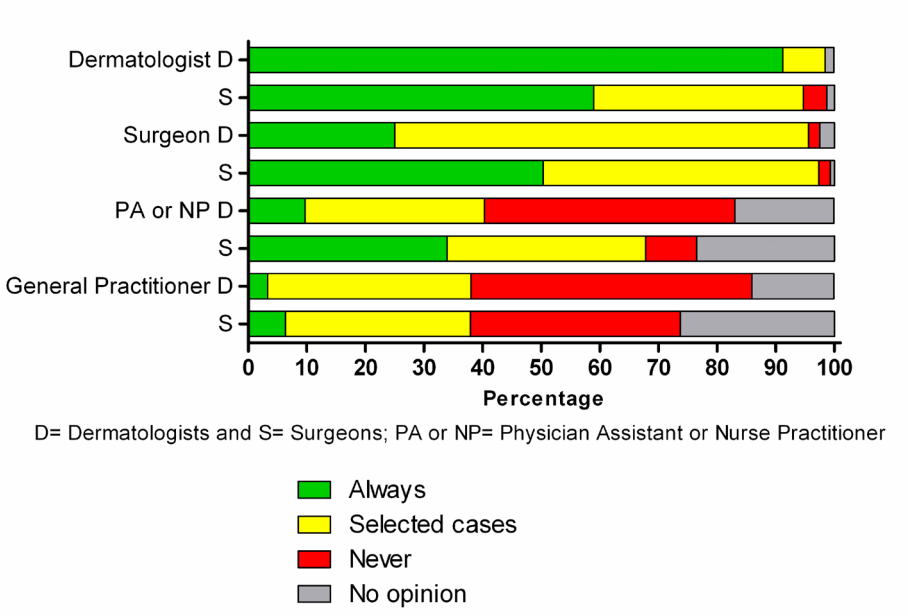

Figure 3. Proposed degree of involvement in follow-up according to Dermatologists and Surgeons

Sentinel lymph node biopsy

Overall, 75% of respondents agreed that the standard diagnostics of cutaneous melanoma does not include a SLNB and that this procedure should be reserved for patients who want to be optimally informed about their prognosis. Sixty-nine percent of surgeons agreed with this versus 80% of dermatologists (p=0.012). When asked for which Breslow thickness there is an indication for SLNB, 2% responded all melanomas regardless of Breslow thickness, 61% answered all melanomas thicker than 1 mm, and 37% answered melanomas between 1.0 and 4.0 mm thickness. Forty-three percent of surgeons reported performing SLNB in all nodal regions, 49% only in the groin and the axilla, and 8% stated they never perform SLNB. Five percent of dermatologists stated they performed SLNB in all nodal regions, 6% answered they performed SLNB only in the groin and the axilla, and 89% did not perform SLNB.

Discussion

In this study we investigated the opinions of Dutch surgeons and dermatologists treating melanoma patients on two 'hot items' in melanoma care: melanoma FU and SLNB. The online survey we used obtained a response rate of 37%. This is slightly better than rates obtained by other web based surveys asking medical specialists to participate[4, 5]. With the exception of one, respondents (99.7%) knew the content of the Dutch national melanoma guideline and one-third stated that they always adhered to the guideline's recommendations. However, two-thirds stated to reported incidental deviations from the guideline. Overall, the highest numbers of respondents agreed that detection of recurrences and secondary primaries are a purpose of FU. Although two-thirds of respondents believe that early detection of recurrent melanoma improves the chance for cure, 42% of respondents believe that the frequency of FU, as prescribed by the current guideline, could be reduced. Three-quarters of specialists have the opinion that SLNB does not belong to the standard diagnostics of cutaneous melanoma, even though it is part of the seventh American Joint Committee on Cancer (AJCC) staging system[7].

Follow-up

- *Purpose and goals*

Detection of a local recurrence and a second primary melanoma were considered by the vast majority of respondents to be a purpose of FU. This suggests that these two objectives were considered to be the most important reasons for routine melanoma FU visits by Dutch medical specialists. Comparable percentages of surgeons and dermatologists agreed on the importance of four of the seven FU purposes. However, fewer surgeons than dermatologists agreed that detection of second primaries and detection of regional and distance metastasis is a purpose of FU. In contrast, fewer dermatologists than surgeons reported that research would be a purpose of FU. The cause for these differences in focus on FU purpose is not clear. It may reflect that dermatologists more than surgeons habitually inspect the whole body to screen for lesions, whereas surgeons may tend to focus on the primary site and the regional nodal basin.

- *Frequency of visits*

According to 42% of respondents, FU visits in the first 10 years after diagnosis could be scheduled less frequently than recommended in the current guideline. Only 4% desired a more frequent schedule. Surprisingly, Holterhues et al. showed that a substantial proportion of Dutch melanoma patients received more frequent FU than recommended by the present guideline.[8] Therefore, better adherence to the guideline combined with a less frequent FU schedule could significantly reduce overconsumption, increase cost-effectiveness, reduce demand on health care resources, and lower patients anxiety levels potentially linked to hospital visits[9, 10].

It has been found that most recurrences (about three-quarters) are detected by the patient rather than by the professional during a FU visit[11-13]. Also, the frequency of FU visits does not seem to affect survival or quality of life[14, 15]. These two points support a reduction in number of FU visits. Thirdly, a recent study showed that the estimated time gain for detection of a recurrence or second primary due to the current high frequency FU, compared to a less intensive FU, is very small.[16] A less frequent FU schedule is proposed in the 2012 draft version of the new Dutch melanoma skin cancer guideline.

- *Responsibility*

The majority of respondents stated that the dermatologist and/or the surgeon are and should be responsible for FU of melanoma patients, either always or in select cases.[3] This is conforming to most melanoma guidelines. Some studies suggest that GP-led FU is feasible[10, 17, 18] However, 43% of respondents discouraged involvement of the GP in Dutch melanoma FU. Also, 26% of respondents disapproved of the involvement of a physician assistant or nurse practitioner. Thus, dermatologist and to a somewhat lesser extent surgeons want to remain responsible for melanoma FU and seem not yet ready to hand this task over to the GP or to nurse practitioners and physician assistants. This is remarkable because it has been suggested that these latter professionals could well be integrated in FU for other malignancies[19, 20], thereby reducing medical specialists' workload and increasing cost-effectiveness.

Responsibility for FU may depend on the stage of disease. For instance, the dermatologist could perform FU in stage I and II melanoma patients while a surgical oncologist could be involved in the FU of patients having more advanced disease, because of the higher probability of diagnostic imaging and operative interventions. It may be that the current shift towards a disease-centered approach in larger hospitals in the Netherlands, with close collaboration between surgeons, dermatologists, and physician assistants or nurse practitioners, will bring new insights into how to manage FU responsibility.

Hospital volume

In this study, 39% of responding surgeons and 19% of dermatologists reported a low number (fewer than 30) of new melanoma patients presenting to their hospital annually. The association of hospital volume with outcomes of advanced surgical procedures is well-known.[21] It could be hypothesized that hospitals treating melanoma patients need to see at least 30 new melanoma patients annually (entailing roughly six recurrences)[14] in order to have enough experience with surgical procedures such as SLNB and lymph node dissections. The Dutch collaborative group for cancer specialists (SONCOS)[22] stated in their quality framework of 2011 that, in order to secure high quality care for cancer patients, hospitals treating melanoma patients are required to: 1) have a minimum of two surgeons experienced in performing SLNB in all nodal basins, 2) perform at least 20 deep groin dissections and 3) treat 20 patients systemically each year. Smaller hospitals not reaching these numbers of melanoma patients should refer to a larger clinic or a melanoma center to optimize outcomes. Following these quality requirements, it might be concerning to find that 49% of surgeons reported that they perform SLNB only in the groin and axilla. These surgeons should consult a head and neck surgeon for patients with a melanoma located in the head and neck region.

Sentinel lymph node biopsy

At the time of questionnaire completion, 75% of respondents agreed with the guideline's recommendation that excludes SLNB from the standard diagnostic path for melanoma. Despite its incorporation into the AJCC melanoma staging manual in 2002, the Dutch specialists, endorsed by the content of the 2005 national guideline, seem to remain predominantly conservative in their opinion about the use of SLNB and the prognostic advantage of this procedure. This finding is reflected by the results of a recent analysis of 2111 patients from the northern part of the Netherlands with a melanoma thicker than 1 mm: fewer than half of these patients underwent SLNB, even in the most recent years.[23] The fourth interim analysis of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) suggest a 7% (78% versus 71%) benefit in 10-year melanoma-specific survival for patients undergoing SLNB.[24] Faster adjustment of both the Dutch medical specialists' attitude and the Dutch guideline to the SLNB is required if this survival benefit persists in the final MSTL-I analysis.

Limitations

The response rate (37%) in the present study is rather low, although comparable with response rates obtained in other web based surveys asking specialists to participate. This may affect the representativeness of the sample. Moreover, this study does not include the points of view of medical specialists other than surgeons and dermatologists, such as physician assistants, nurse practitioners, or GPs. Finally, the survey did not record the rationale respondents had for their point of view.

Future perspectives

A considerable proportion of medical specialists believe the frequency of melanoma FU visits in the Netherlands could be reduced. If the results of the current Dutch melanoma follow-up (MELFO) trial[25] confirm the feasibility and safety of reduced and patient-tailored FU schedules, the rising demand on health care resources can be decreased by strict compliance with new FU guidelines. Furthermore, patient-tailored FU can be accompanied by improvements in patients' knowledge of melanoma through education using instruction videos on self-examination and by the development of cancer survivorship plans to increase recurrence detection by patients and reduce their need for FU visits. Therefore, in collaboration with the Dutch Cancer Foundation, the University Medical Center Groningen developed instruction videos that can be viewed online (http://www.youtube.com/watch?v=P5qKpCjXaLA and http://www.youtube.com/watch?v=dfP995HvBLA).

Additionally, combined FU by dermatologist and surgical oncologist in a disease-centered (e.g. melanoma clinic) approach may further increase quality and cost-effectiveness. The majority of respondents stated that FU was and should be performed by both dermatology and surgical oncology. Views on these subjects could change considerably among the surveyed population if recent breakthroughs in medical treatment of recurrent melanoma (ipilimumab and vemurafenib)[26, 27] are demonstrated to have a true effect on survival. In that case, early detection with subsequent medical treatment for recurrences might improve survival and therefore the frequency and content of FU might also stronger influence survival.

In the present situation, however, a disease-centered approach in high volume centers with less frequent FU could increase cost-effectiveness of melanoma care and seems to be supported by at least a reasonable proportion of Dutch medical specialists.

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Chapter 6

Therapeutic lymph node dissection in melanoma: different prognosis for different macrometastasis sites?

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ABSTRACT

Background. The prognostic significance of primary tumor location, especially the worse prognosis for melanomas in the scalp and neck region, is well established. However, the prognosis for different sites of nodal macrometastasis has never been studied. This study investigated the prognostic value of the location of macrometastasis in terms of recurrence and survival rates after therapeutic lymph node dissection (TLND).

Methods. All consecutive FDG-PET-staged melanoma patients with palpable and cytologically proven lymph node metastases operated at our clinic between 2003 and 2011 were included. Disease-free survival (DFS) and disease-specific survival (DSS) were compared for nodal metastases in the groin, axilla, and neck regions using multivariable analysis.

Results. A total of 149 patients underwent TLND; with 70 groin (47%), 57 axillary (38%), and 22 neck (15%) dissections. During a median follow-up of 18 (range 1–98) months, 102 patients (68%) developed recurrent disease. Distant recurrence was the first sign of progressive disease in 78%, 76%, and 55% of the groin, axilla, and neck groups, respectively (p=0.26). Low involved/total lymph nodes (L/N) ratio (p<0.001) and absence of extranodal growth pattern (p=0.05) were independent predictors of a longer DFS. For DSS, neck site of nodal metastasis (p=0.02) and low L/N ratio (p<0.001) were independent predictors of long survival. The estimated 5-year DSS for the groin, axilla, and neck sites was 28%, 34%, and 66%, respectively.

Conclusion. There seems significantly longer DSS after TLND for nodal macrometastases in the neck compared to axillary and groin sites, although larger series should confirm this finding.

Background

The incidence of melanoma continues to increase in the Western world. In the Netherlands, the incidence doubled over the past two decades, to 26.3 per 100,000 in 2009 from 11.3 per 100,000 in 1989.[1, 2] Most patients present initially with Stage I or II melanoma.[3] Unfortunately, despite defined surgical treatment of the primary melanoma with excision margins of 1 or 2 cm, approximately 16–28% of patients develop recurrent disease. These recurrences occur locally or in-transit in 20–28%, distant in 15–50%, but most frequently in regional lymph nodes (26–60%).[4]

When nodal recurrence is detectable clinically (stage IIIB-C), patients may benefit from therapeutic lymph node dissection (TLND) with or without adjuvant radiation treatment in terms of regional tumor control and survival, resulting in a 5-year survival rate of 29–52%.[3, 5-9] Major predictors of an unfavourable prognosis are greater Breslow thickness, the presence of ulceration, and a high mitotic rate. The Clark level, the location of the primary melanoma, age, and sex are less important predictors.[3, 10] The prognostic significance of primary melanoma characteristics can not be identified for patients with nodal metastasis undergoing TLND.[5] For this group of patients, a recent study showed that a preoperatively elevated S-100B tumor marker had a negative prognostic value.[11]

The prognostic significance of primary tumor location, especially worse prognosis for melanomas in the scalp and neck region, is well established.[12, 13] However, the prognostic value of the anatomical location of nodal recurrence in stage IIIB-C melanoma has not previously been investigated. Patients with nodal metastasis are at high risk for distant metastasis. Therefore, stage III melanoma patients with palpable lymph node metastases are staged by whole body FDG-PET and spiral CT at our center in the last decade, avoiding unnecessary surgery in the presence of systemic disease in 15.5% of these patients.[14]

The aim of the present study was to analyse the site of recurrence, the disease-free survival (DFS), and the disease-specific survival (DSS) according to the anatomical location of lymph node metastasis (groin, axilla, and neck) in optimally staged patients with melanoma stage IIIB-C.

Patients and Methods

All consecutive melanoma patients with palpable and cytologically proven lymph node metastases diagnosed at the Division of Surgical Oncology of the University Medical Center Groningen (UMCG), the Netherlands, between 2003 and 2011 underwent staging with whole-body FDG-PET and spiral-CT. All patients were informed about their stage of disease, type of regional nodal dissection, and potential perioperative complications, according to the UMCG standards. Those with distant metastases or with more than one affected lymph node basin were excluded from this study. A total of 149 stage IIIB-C melanoma patients underwent a therapeutic lymph node dissection. In this group, only 7 patients had been staged previously using sentinel lymph node biopsy (SLNB), which was negative in 6 cases. The single patient with a positive SLNB refused a proposed completion lymph node dissection (CLND) at the time and recurred later in the affected regional lymph node basin.

All therapeutic dissections were performed by experienced surgical oncologists. A level I-III axillary dissection was performed with resection of the minor pectoral muscle. Groin dissection comprised superficial (inguinal) and deep (iliac and obturator) lymph node dissection with sartorius muscle transposition.[15] Neck dissection included radical removal of lymph nodes in levels I-III, I-V, and II-V, including the posterior compartment depending on indication. A subtotal dissection of the parotid gland was performed depending on the localization of the lymph node metastasis and the primary site.

Patients with positive lymph nodes larger than 3 cm, 3 or more positive lymph nodes, and/or extranodal growth pattern received adjuvant radiotherapy (45-60 Gy).[16, 17] All patients with recurrence after TLND were discussed in a multidisciplinary melanoma conference and received what is termed a 'tailored treatment' i.e. surgery, radiation, and/or systemic treatment according to the current standard or experimental treatment protocols.

Statistical analysis

Characteristics of the patient (sex and age), primary melanoma (Breslow thickness, Clark level, ulceration, mitotic rate, and primary site), and lymph node metastasis (interval to metastasis, extranodal growth pattern, total number of nodes, number of involved nodes, involved/total lymph nodes (L/N) ratio, and size of the largest nodal metastasis) were recorded and analyzed for differences between the groin, axillary, and neck groups. Fischer's exact test or the Chi squared test for categorical variables and the Kruskal-Wallis test for continuous variables were used to analyze the differences using a significance level of 5%. DFS and DSS were calculated from the date of the TLND. Univariate and multivariable Cox Proportional Hazards Analysis were used to assess DFS and DSS for different nodal metastasis locations, with an event defined as any recurrence for DFS and death due to melanoma for DSS. All factors significant at a 10% significance level in univariate analysis were included in a multivariable model along with sex, age, Breslow thickness, and ulceration. Quantitative characteristics were entered as continuous variables in univariate and multivariable analysis on DFS and DSS. Because of its prognostic significance we used the L/N ratio rather than the number of involved nodes for multivariable analysis.[18-20] A backward stepwise method was used subsequently to identify independent predictors for DFS and DSS on a 5% significance level.

Results

A total of 149 patients underwent TLND. There were 70 groin dissections (47%), 57 axillary dissections (38%), and 22 neck dissections (15%). The median age was 58 (range 16-93) years and 64 patients (43%) were female.

Significant differences in characteristics between the three lymph node basin groups were found for sex ($p=0.001$, with more males in the axilla and neck groups), Clark level ($p=0.05$, lower in neck group), total number of harvested nodes ($p=0.04$, higher in neck group) and size of largest lymph node metastasis on pathological examination ($p<0.001$, with smaller metastases in the neck group). (Table 1)

Table 1. Patient characteristics according to location of lymph node metastasis

Variable	No. of patients (%)			
	Groin	**Axilla**	**Neck**	**p-value**
Sex				
Female	41 (59)	19 (33)	4 (18)	**0.001**
Male	29 (41)	38 (67)	18 (82)	
Age (years)				
Median (range)	58 (29-87)	53 (25-93)	59 (16-82)	0.26
<50	17 (24)	24 (42)	7 (32)	
50-64	32 (46)	19 (33)	5 (23)	
65+	21 (30)	14 (25)	10 (45)	
Breslow thickness (mm)				
Median (range)	2.1 (0.1-16)	1.8 (0.4-8)	2.5 (0.5-14)	0.51
T1 (<1.00)	6 (9)	9 (16)	3 (13)	
T2 (1.00-2.00)	24 (34)	18 (32)	5 (23)	
T3 (2.00-4.00)	26 (37)	15 (26)	5 (23)	
T4 (>4.00)	9 (13)	7 (12)	5 (23)	
Unknown	5 (7)	8 (14)	4 (18)	
Clark Level				
II / III	10 (17)	11 (26)	6 (32)	**0.05**
IV / V	45 (75)	26 (62)	7 (36)	
Unknown	5 (8)	5 (12)	6 (32)	
Unknown primary melanoma				
No	67 (96)	52 (91)	19 (86)	0.27
Yes	3 (4)	5 (9)	3 (14)	
Ulceration				
Absent	42 (60)	30 (52)	14 (64)	0.16
Present	24 (34)	18 (32)	2 (9)	
Unknown	4 (6)	9 (16)	6 (27)	
Mitotic rate per mm^2				
Median (range)	5 (0-18)	4 (0-21)	4 (1-35)	0.89
<5	28 (40)	28 (49)	8 (36)	
≥5	29 (41)	19 (33)	6 (28)	
Unknown	13 (19)	10 (18)	8 (36)	
Interval primary – nodal metastasis (years) [a]				
Median (range)	2.1 (0-17)	1.9 (0-15)	1.2 (0-19)	0.65
≤2 years	32 (48)	28 (54)	11 (58)	
>2 years	35 (52)	24 (46)	8 (42)	
Extranodal growth pattern				
No	36 (51)	39 (68)	12 (54)	0.14
Yes	34 (49)	18 (32)	10 (46)	
Total no of Nodes				
Median (range)	15 (2-38)	16 (6-43)	24 (3-70)	**0.04**
Number of involved nodes				
Median (range)	3 (1-23)	2 (1-25)	2 (1-10)	0.27
N1 (1)	21 (30)	25 (44)	8 (36)	
N2 (2-3)	22 (31)	15 (26)	7 (32)	
N3 (4+)	27 (39)	7 (32)	7 (32)	

***Table 1** continued. Patient characteristics according to location of lymph node metastasis*

Variable	No. of patients (%)			
	Groin	**Axilla**	**Neck**	**p-value**
Ratio of involved / total nodes (%)				
Median L/N ratio (range)	15 (3-100)	15 (2-100)	10 (1-67)	0.12
≤10	24 (34)	24 (42)	11 (50)	
10-25	19 (27)	18 (32)	8 (36)	
>25	27 (39)	15 (26)	3 (7)	
Size of nodal metastasis (cm)				
Median (range)	2.8 (0.1-7.0)	5.0 (1.5-9.0)	2.2 (0.3-6.0)	**<0.001**
<3.0	35 (50)	14 (25)	16 (73)	
≥3.0	33 (47)	41 (72)	5 (23)	
Unknown	2 (3)	2 (3)	1 (4)	
AJCC Stage [b]				
IIIB	26 (37)	26 (46)	14 (64)	0.09
IIIC	44 (63)	31 (54)	8 (36)	
Follow up (months)				
Median (range)	19 (1-93)	16 (1-98)	43 (3-94)	**0.05**

[a] Unknown primary melanoma not included in calculation of interval.
[b] According to the 7th melanoma classification of the American Joint Committee on Cancer.

Site of recurrence

One hundred two patients (68%) developed recurrent disease during follow-up. As shown in Table 2, a large proportion of patients in the groin and axilla groups had recurrent disease and presented with distant metastases as the first sign of progressive disease (78% and 76%). In the neck group, only 55% of patients presented with a distant metastasis as the first site of recurrence (p=0.26).

Table 2. Site of first recurrence after therapeutic lymph node dissection according to location of the lymph node metastasis

Recurrence*	No. of patients (%)			
	Local	**Locoregional**	**Distant**	**p-value**
Groin	2 (4)	10 (18)	42 (78)	0.26
Axilla	4 (11)	5 (13)	28 (76)	
Neck	1 (9)	4 (36)	6 (55)	

* Patients presenting with both local or locoregional and distant recurrences were classified as distant.

Recurrence and survival rates

The follow-up for the entire group was 18 (range 1–98) months with an estimated 5-year DFS of 27% (95% CI: 19–34%) and an estimated 5-year DSS of 37% (95% CI: 28–45%). The estimated 5-year DFS for the groin, axilla, and neck groups was 12%, 27%, and 49%, respectively (Figure 1a). Variables associated with DFS in univariate analysis were presence of ulceration, the location of nodal metastasis, extranodal growth pattern, L/N ratio, and the size of the largest nodal metastasis. Neck location of the metastasis showed a significantly longer DFS in univariate analysis. (Table 3) The multivariable model showed a lower L/N ratio ($p<0.001$) and absence of extranodal growth pattern ($p=0.05$) to be independent predictors of longer DFS. The association of the location of lymph node metastasis with DFS was not statistically significant in the multivariable model (Table 4).

The estimated 5-year DSS was 28%, 34%, and 66% for groin, axilla, and neck, respectively (Figure 1b). Variables associated with DSS in univariate analysis were the location of nodal metastasis, extranodal growth pattern, L/N ratio, and the size of the largest nodal metastasis (Table 3). The multivariable model for DSS revealed neck site of metastasis ($p=0.02$) (Table 4) and a lower L/N ratio ($p<0.001$) to be significantly associated with better survival.

Table 3. Univariate Cox regression analysis of prognostic factors for disease-free survival and disease-specific survival

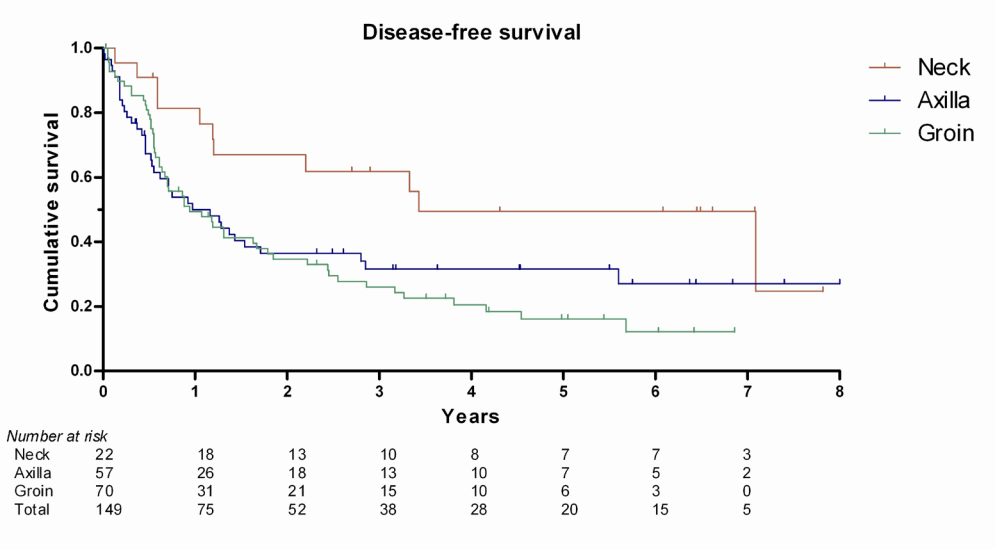
	DFS			DSS		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Sex						
Female	1			1		
Male	1.07	0.72-1.59	0.73	1.28	0.83-1.98	0.26
Age (years)						
Continuous	0.99	0.98-1.00	0.15	1.00	0.98-1.01	0.70
<50	1			1		
50-64	0.93	0.58-1.49		1.07	0.64-1.80	
65+	0.88	0.54-1.43		1.15	0.67-1.99	
Breslow thickness (mm)						
Continuous	0.98	0.89-1.07	0.60	0.98	0.89-1.09	0.74
T1 (<1.00)	1			1		
T2 (1.00-2.00)	0.79	0.40-1.56		1.10	0.50-2.42	
T3 (2.00-4.00)	1.09	0.56-2.09		1.17	0.53-2.57	
T4 (>4.00)	0.73	0.33-1.61		0.86	0.35-2.15	
Clark Level						
II	1			1		
III	1.77	0.41-7.70	0.46	3.71	0.48-28.5	0.21
IV	2.55	0.63-10.44	0.20	4.86	0.67-35.2	0.12
V	2.29	0.46-11.34	0.32	3.60	0.40-32.4	0.25
Unknown primary melanoma						
No	1			1		
Yes	1,66	0.72-3.83	0.23	1.29	0.56-2.97	0.55

Table 3 *continued. Univariate Cox regression analysis of prognostic factors for disease-free survival and disease-specific survival*

Variable	DFS HR	95% CI	p-value	DSS HR	95% CI	p-value
Location primary melanoma						
Arm	1			1		
Leg	1.64	0.77-3.49	0.20	1.55	0.68-3.53	0.29
Trunk	1.42	0.65-3.08	0.37	1.59	0.69-3.67	0.28
Head/neck	0.54	0.19-1.57	0.26	0.56	0.17-1.73	0.31
Ulceration						
Present	1			1		
Absent	0.64	0.42-0.99	**0.05**	0.72	0.44-1.16	0.18
Mitotic rate per mm²						
Continuous	1.00	0.97-1.04	0.86	1.00	0.96-1.05	0.84
<5	1			1		
≥5	1.19	0.76-1.87		1.13	0.69-1.86	
Interval primary– nodal metastasis (years)						
Continuous	0.95	0.90-1.01	0.11	0.90	0.88-1.01	0.09
Location metastasis						
Groin	1			1		
Axilla	0.84	0.55-1.28	0.42	0.99	0.63-1.56	0.97
Neck	0.42	0.22-0.81	**0.009**	0.34	0.15-0.77	**0.009**
Extranodal growth pattern						
No	1			1		
Yes	1.96	1.33-2.90	**0.001**	1.86	1.21-2.85	**0.004**
No of involved nodes						
Continuous	1.06	1.03-1.10	**0.001**	1.07	1.03-1.12	**0.001**
N1 (1)	1			1		
N2 (2-3)	1.32	0.76-2.31		0.99	1.56-1.74	
N3 (4+)	2.42	1.42-4.11		2.33	1.40-3.88	
Ratio of involved/total nodes (%)						
Continuous	1.02	1.01-1.02	**<0.001**	1.01	1.01-1.02	**<0.001**
≤10	1			1		
10-25	1.27	0.73-2.22		1.25	0.71-2.18	
>25	2.30	1.37-3.88		2.69	1.60-4.52	
Size of the lymph node metastasis (cm)						
Continuous	1.14	1.02-1.26	**0.02**	1.17	1.05-1.31	**0.004**
<3.0	1			1		
≥3.0	1.40	0.94-2.09		1.71	1.09-2.68	

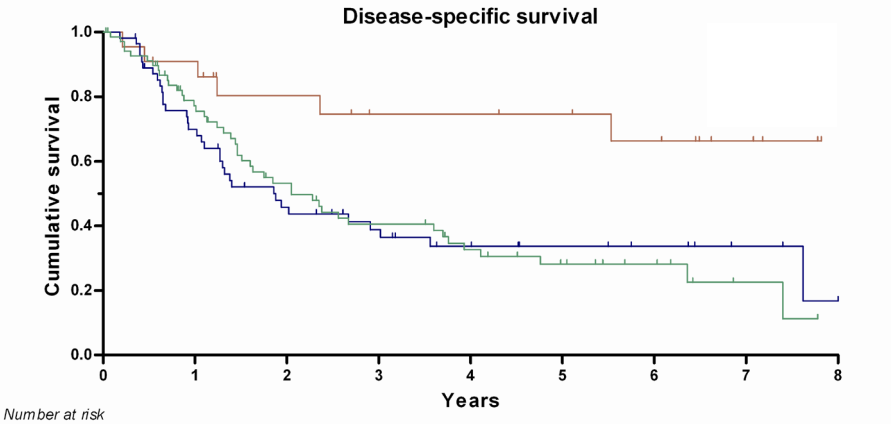
All variables with p<0.10 were included in multivariable model along with sex, age, Breslow thickness, and ulceration.

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival.



Number at risk

Neck	22	18	13	10	8	7	7	3
Axilla	57	26	18	13	10	7	5	2
Groin	70	31	21	15	10	6	3	0
Total	149	75	52	38	28	20	15	5



Number at risk

Neck	22	19	14	11	11	10	8	4
Axilla	57	36	22	16	11	8	6	3
Groin	70	47	30	22	16	11	7	2
Total	149	102	66	49	38	29	21	9

Figure 1a/b. Kaplan-Meier for disease-free survival (1a) and disease-specific survival (1b) according to location of lymph node metastasis

Table 4. Multivariable Cox regression analysis of prognostic value of nodal metastasis location for disease-free survival and disease-specific survival

	DFS			DSS		
Location	**5-year DFS** % (95% CI)	**Multivariable[a]** HR (95%CI)	**p-value**	**5-year DSS** % (95%CI)	**Multivariable[b]** HR (95%CI)	**p-value**
Groin	12.1 (2.1-22.1)	1 (reference)		28.2 (16.0-40.3)	1 (reference)	
Axilla	27.1 (13.4-40.8)	0.94 (0.59-1.50)	0.78	33.6 (19.9-47.3)	0.98 (0.60-1.60)	0.93
Neck	49.2 (26.5-71.9)	0.48 (0.22-1.09)	0.08	66.3 (43.2-89.4)	0.27 (0.10-0.79)	**0.02**

[a] Hazard ratio for DFS adjusted for presence of ulceration, extranodal growth pattern, and ratio of involved/total nodes (L/N ratio).
[b] Hazard ratio for DSS adjusted for sex and L/N ratio.
Abbreviations: DFS, disease-free survival; DSS, disease-specific survival.

Discussion

Analysis of 149 melanoma patients undergoing curative TLND showed the 5-year DSS to be 37% for the entire group, which is similar to percentages reported in the literature.[5, 21] Univariate and multivariable analysis revealed differences in prognosis for metastasis in the groin, axilla, or neck. Specifically, nodal metastasis located in the neck was associated with significantly better DSS. No statistically significant difference was found for frequency of distant metastases as the first site of recurrence: groin group 78%, axilla group 76%, and neck group 55% (p=0.26).

In present study, significant prognostic factors for survival in univariate analysis were site of nodal metastasis, extranodal growth pattern, L/N ratio, and size of the largest nodal metastasis. Besides neck site of nodal metastasis, low L/N ratio was found to be an independent predictor for better DSS which is in agreement with recent literature.[18-20] Primary melanoma characteristics were not associated with survival, which is consistent with the study of 441 Stage IIIB-C melanoma patients by Balch et al.[3, 5] Finding longer survival for neck site metastasis seems contrary to the observation that head and neck melanomas have a worse prognosis than melanomas at other sites.[12, 13] However, the literature currently lacks specific studies regarding the prognostic value of the site of nodal metastasis. Moreover, a recent study on the outcome of TLND in stage III melanoma patients with an unknown primary melanoma did notice a survival benefit for patients with a neck metastasis compared to groin or axillary metastasis.[21]

The better prognosis for patients with neck metastasis could be explained by earlier detection of nodal metastasis, resulting in a smaller tumor burden at time of the TLND, and of recurrent locoregional disease in the neck, because of the more superficial and notable position of nodes compared to those in the groin or axilla. Supporting this, we found that the lymph node metastases in the neck group were significantly smaller than in the groin and axilla groups. In addition, there is a tendency for patients in the neck group to present more frequently with local or locoregional recurrence as the first sign of progressive disease, rather than distant disease, compared to the groin and axilla groups. However,

with the current study size, this tendency did not reach statistical significance.

To evaluate the outcomes of nodal metastasis at different locations without the detection benefit of superficial macrometastasis, we performed a subanalysis of data of 117 patients that underwent CLND shortly after positive SLNB in a recently published study by de Vries et al.[22] This subanalysis showed a 5-year DSS of 63%, 68 %, and 75% for the groin, axilla, and neck groups respectively. Although the difference in survival was not statistically significant, the more favorable number for metastasis at the neck site is notable. Therefore we concluded that the detection benefit alone, even though it proved to be important, could not fully explain the survival difference. Another hypothesis that could explain our findings is the effect of a more extensive lymphatic system in the neck region, which could keep metastases from hematogenous spread. In this case, we would expect differences in the percentage of patients that were upstaged with PET or CT after presenting with palpable lymph node metastases at the different locations. However, in a previous study we found no differences in the percentage of upstaging between the groups of patients with groin, axilla or neck metastases (18.3% groin, 31.3% axilla, and 23.3% neck; p=0.12).[14] The exact mechanisms underlying better survival thus remain unknown. However, possibilities include differences in the behavior of the primary melanoma, a lower detection threshold, immunological advantages of the nodal basin in the neck, and dissection effects.

The findings of this study are limited by the rather small group of patients that underwent TLND of the neck (n=22). Therefore, definitive establishment of the more favorable prognosis for macrometastasis when located in the neck needs confirmation by larger series.

In conclusion, this study showed better prognosis after TLND for stage IIIB-C melanoma when the lymph node metastasis is located in the neck compared to axillary and groin sites.

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Chapter 7

S-100B: a stronger prognostic biomarker than LDH in stage IIIB-C melanoma

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ABSTRACT

Introduction. In melanoma patients with nodal macrometastases, distinction between good and poor prognosis is based on the presence of primary melanoma ulceration or metastatic involvement of 4 or more lymph nodes in the 7th AJCC classification. We hypothesized that biomarkers would increase the accurateness of staging in these patients. The aim was to assess and compare the prognostic impact of biomarkers S-100B and LDH and to determine the best timing of their measurement in stage IIIB-C melanoma.

Methods. A total of 119 patients underwent therapeutic lymph node dissection (TLND) for nodal macrometastases with serum S-100B and LDH level measurements preoperatively. In 75 of them, S-100B and LDH was also measured on postoperative days 1 and 2. S-100B and LDH levels on days 0, 1, and 2 were compared for their association with disease-free survival (DFS) and disease-specific survival (DSS).

Results. At a median follow-up of 17 (range 1-89) months, S-100B levels at all time points were associated with DFS. In multivariable analysis, preoperative S-100B and S-100B measured on day 2 showed the strongest association with DFS (HR=2.55, p=0.007 and HR=3.80, p=0.01). For DSS, the preoperative S-100B level was the strongest independent predictor (HR=2.81, p=0.01). LDH measurements showed a significant association with DSS in univariate analysis, only when measured preoperatively (HR=2.46, p=0.01). In multivariable analysis, LDH measurement was not associated with melanoma prognosis.

Conclusion. The S-100B level measured preoperatively is, in contrast to LDH, one of the most important independent predictors of melanoma prognosis in patients undergoing TLND for nodal macrometastases.

Introduction

The incidence of melanoma in the western world is on the rise. In the United States, estimated more than 70,000 people will be diagnosed with melanoma in 2012.[1] The majority of patients present initially with Stage I or II melanoma and 33-50% of these patients are diagnosed with Stage IA disease.[2, 3]

Unfortunately, approximately one out of five melanoma patients develops recurrent disease. These recurrences occur locally or in-transit in 20–28%, distant in 15–50%, but most frequently in regional lymph nodes (26–60%).[4] Patients with palpable lymph node metastases, American Joint Committee on Cancer (AJCC) stage IIIB-C, have a 5-year survival rate of 43% when a regional therapeutic lymph node dissection (TLND) of the affected basin is performed.[5] In patients with palpable lymph node metastases, distinction between a relatively good and poor prognosis (stage IIIB and IIIC, respectively) is, in the current 7th AJCC melanoma classification, based on the presence of primary melanoma ulceration or metastatic involvement of 4 or more lymph nodes.

For melanoma, two biomarkers have been extensively studied: earlier Lactate Dehydrogenase (LDH) and lately S-100B.[6] LDH was already implemented in the AJCC system in 2001 to classify stage IV patients. The melanoma associated molecule S-100B was found to be correlated with melanoma progression in both stage III and IV disease[7, 8]. Previously our institution established that elevated levels of serum S-100B are associated with a decreased disease-free survival in melanoma patients presenting with palpable nodal metastases (stage IIIB-C).[9] Also Bouwhuis et al. and Tarhinni et al. proved S-100B to be a prognostic marker for survival in melanoma.[10, 11] However, today's use of biomarkers in melanoma still only includes LDH as a staging marker in AJCC stage IV disease and the best timing of perioperative S-100B measurements is unknown.

We hypothesized that biomarkers could increase the accurateness of staging in patients with nodal macrometastases (currently AJCC stage IIIB–C). Identification of patients with macrometastases with high risk for recurrence seems to become more and more important with the recent breakthroughs in medical treatment of recurrent melanoma (e.g., with ipilimumab and vemurafenib).[12,13] In the very near future, biomarkers can be used to select high risk stage III patients for adjuvant systemic treatment in new trials. For example, the upcoming COMBI-AD trial will study the effect of adjuvant MEK and BRAF inhibition in surgically treated stage III melanoma patients.[14]

The aim of the present study was to (re)assess and compare the prognostic impact of the biomarkers S-100B and LDH in current stage IIIB-C melanoma at our institution with a larger patient cohort and prolonged follow-up. Also, different time points of perioperative S-100B and LDH measurements were compared for their association with melanoma prognosis.

Methods

All consecutive melanoma patients with palpable and cytologically proven lymph node metastases diagnosed at and referred to the Division of Surgical Oncology of the University Medical Center Groningen (UMCG), the Netherlands, between 2004 and 2011 underwent staging with whole-body FDG-PET and/or spiral-CT. Patients with distant metastases or more than one affected lymph node basin were excluded from this study. All patients were informed about their stage of disease, type of regional nodal dissection, and potential perioperative complications, according to the UMCG standards. All stage IIIB-C melanoma patients underwent TLND and had S-100B and LDH biomarker levels measured one day prior to surgery and on postoperative days 1 and 2 if patients were still hospitalized.

A level I-III axillary dissection was performed with resection of the minor pectoral muscle. Groin dissection comprised superficial (inguinal) and deep (iliac and obturator) lymph node dissection with sartorius muscle transposition.[15] Neck dissection included radical removal of lymph nodes in levels I-III, I–V, and II-V, including the posterior compartment depending on indication. A subtotal dissection of the parotid gland was performed depending on the localization of the lymph node metastasis and the primary site. Patients with positive lymph nodes larger than 3 cm, 3 or more positive lymph nodes, and/or extranodal growth pattern received adjuvant radiotherapy (45–60 Gy).[16,17]

All patients with recurrent disease after TLND were discussed in a multidisciplinary melanoma conference and received what is termed a 'tailored treatment' i.e. surgery, radiation, and/or systemic treatment according to the present standard or experimental treatment protocols.

Biomarker assay and reference cutoff

S-100B levels were calculated on the basis of a calibration curve and checked against internal standards with a known concentration of S-100B. Initially the Diasorin S-100b assay (Sangtec 100 Diasorin, Saluggia, Italy) was performed on the Advantage immunoassay platform (Nichols). However, this Nichols analyzer was abruptly withdrawn from all laboratories worldwide, forcing laboratories to change to other assays. Our laboratory changed to and validated the manually performed S-100B assay of the same firm (Diasorin). In this validation process a new cut-off was determined by analyzing S-100B levels of 120 healthy individuals according to the CLSI C28A2 guideline. This resulted in a reference cutoff point of 0.15 µg/l for measurements before July 2006 and 0.20 µg/l for measurements after July 2006 at our institution.

LDH was analyzed routinely by means of Roche Modular (Hitachi) with an enzymatic activity measurement; normal levels of LDH were considered to be below the reference cutoff of 250 U/l.

Statistical analysis

The clinicopathologic characteristics of all 119 patients and their primary melanomas (age and sex, histologic subtype, unknown primary, Breslow thickness, Clark level, ulceration, mitotic rate, and regression), and the pathologic characteristics of their TLND specimens (total number of nodes, number of involved nodes, lymph node (LN) ratio, size of the largest nodal metastasis, and extranodal growth pattern) were analyzed for their association with disease-free survival (DFS) and disease-specific survival (DSS) using univariate Cox regression analysis. Subsequently, the prognostic value of S-100B and LDH levels on the preoperative and postoperative (day 1 and 2) days was compared in the 75 patients who had complete data at all time points. Also, the prognostic value of the perioperative biomarker change, from preoperative to day 2, was assessed. Biomarker levels that were significantly associated with DFS and DSS in univariate analysis were entered in a multivariable model together with clinicopathologic factors that were associated with DFS and DSS on a 5% significance level. Kaplan-Meier curves were created for the strongest prognostic combinations of the biomarkers and their measurement timing. Statistical analysis was performed using the SPSS software package (SPSS 18.0, Chicago, Illinois, USA).

Results

In a total of 119 patients, 56 females and 63 males with a median age of 58.3 (range 24.7-93.2) years underwent a TLND with curative intent. In the majority of patients (55.5%) a groin dissection was performed, in 34.5% an axillary dissection, and in 10.1% a neck dissection. (Table 1) Following histopathological analysis, 53 patients were staged as IIIB and 66 as stage IIIC according to the current 7th AJCC melanoma classification. The median follow up of all patients was 17 (range 1-89) months. For the patients still alive the median follow-up was 32 (range 3-89) months.

Clinicopathological characteristics associated with DFS and DSS

In univariate analysis of 119 patients, the presence of ulceration, the number of involved nodes, the LN ratio, and the presence of extranodal growth showed significant association with both decreased DFS and DSS. Male sex and the total number of harvested nodes were the only characteristics that were associated with a decreased DSS. A trend for improved DFS and DSS was found for neck site of nodal metastases compared to the axillary and groin sites. (Table 1)

Table 1. Characteristics of 119 patients undergoing therapeutic lymph node dissection and their association with melanoma prognosis

Characteristic	n	(%)	DFS Univariate HR (p)	DSS Univariate HR (p)
Sex				
Female	56	(47.1)	1	**1**
Male	63	(52.9)	1.43 (0.11)	**2.00 (0.01)**
Age (years)				
Continuous (median, range)	58.3	(24.7-93.2)	1.01 (0.42)	1.01 (0.16)
Histologic type				
Superficial spreading	64	(53.8)	1	1
Nodular	30	(25.2)	0.90 (0.70)	0.69 (0.29)
Acral lentiginous	6	(5.0)	1.79 (0.22)	2.21 (0.10)
Other	2	(1.7)	0.71 (0.73)	1.05 (0.97)
Missing	*12*	*(10.1)*		
Unknown primary				
No	114	(95.8)	1	1
Yes	5	(4.2)	0.85 (0.79)	0.43 (0.40)
Breslow thickness (mm)				
Continuous (median, range)	2.1	(0.5-16.0)	1.02 (0.69)	1.03 (0.56)
T1 (<1.01)	*15*	*(12.6)*		
T2 (1.01-2.00)	*39*	*(32.8)*		
T3 (2.01-4.00)	*37*	*(31.1)*		
T4 (>4.00)	*19*	*(16.0)*		
Missing	*9*	*(7.6)*		
Clark level				
II/III	26	(21.8)	1	1
IV	75	(63.0)	1.07 (0.81)	1.53 (0.23)
V	9	(7.6)	1.36 (0.50)	1.73 (0.32)
Missing	*9*	*(7.6)*		
Ulceration				
No	67	(56.3)	**1**	**1**
Yes	46	(38.7)	**2.18 (0.001)**	**2.14 (0.006)**
Missing	*6*	*(5.0)*		
Mitotic rate				
Quantitative (median, range)	4	(0-23)	1.04 (0.07)	1.02 (0.57)
<5	*59*	*(49.6)*		
≥5	*45*	*(37.8)*		
Missing	*15*	*(12.6)*		
Regression				
No	73	(61.3)	1	1
Yes	17	(14.3)	1.03 (0.33)	1.34 (0.46)
Missing	*29*	*(24.4)*		
Location nodal metastasis				
Groin	66	(55.5)	1	1
Axilla	41	(34.5)	0.86 (0.55)	0.96 (0.88)
Neck	12	(10.1)	0.57 (0.17)	0.38 (0.11)

***Table 1** continued. Characteristics of 119 patients undergoing therapeutic lymph node dissection and their association with melanoma prognosis*

Characteristic	n	(%)	DFS Univariate HR (p)	DSS Univariate HR (p)
Total number of nodes				
Quantitative (median, range)	16	(3-70)	0.98 (0.27)	**0.96 (0.04)**
Number of involved nodes				
Quantitative (median, range)	2	(1-23)	**1.08 (0.001)**	**1.07 (0.04)**
N1 (1)	*48*	*(40.3)*		
N2 (2-3)	*37*	*(31.1)*		
N3 (4+)	*34*	*(28.6)*		
LN ratio				
Continuous (median, range)	12	(1-100)	**1.02 (<0.001)**	**1.01 (0.005)**
≤10	*48*	*(39.5)*		
10-25	*39*	*(32.8)*		
>25	*32*	*(26.9)*		
Size of metastasis (cm)				
Continuous (median, range)	3.4	(0.1-9.5)	1.05 (0.36)	1.07 (0.27)
<3.0	*47*	*(39.5)*		
≥3.0	*65*	*(54.6)*		
Missing	*7*	*(5.9)*		
Extranodal growth				
No	69	(58.0)	**1**	**1**
Yes	50	(42.0)	**1.57 (0.05)**	**1.85 (0.02)**

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LN, lymph node
Italic printed items are descriptive and not included in univariate analysis.
All characteristics with p<0.05 were included in the multivariable analysis in table 2 and 3.

Association of S-100B and LDH at different time points with DFS and DSS

Complete biomarker data was available for analyses in 75 out of 119 patients. For S-100B, elevated serum levels were found in 36.0%, 18,7%, and 9.3%, when measured preoperatively, on day 1, and on day 2, respectively. As shown in Table 2, the S-100B levels at all time points were associated with DFS in both univariate and multivariable analysis. Preoperative S-100B and S-100B measured on day 2 showed the strongest association with DFS in multivariable analysis (hazard ratio [HR] 2.55, 95 % CI 1.29–5.06, P = 0.007 and HR 3.80, 95 % CI 1.38–10.46, P = 0.01, respectively). For DSS, both preoperative S-100B and the S-100B level measured on day 2 were significant predictors in univariate analysis. In multivariable analysis, the preoperative S-100B level showed the strongest association with DSS (HR 2.81, 95 % CI 1.23–6.42, P = 0.01). (Table 2)

The perioperative change of S-100B showed significant association with DFS and DSS in univariate and multivariable analysis, especially for patients in whom serum levels remained normal compared to patients in whom S-100B became normal (Table 2). Five patients in whom S-100B levels remained elevated showed significantly worse DFS. Two of them presented with a regional recurrence and three with distant disease.

For LDH, as shown in Table 2, elevated levels were found in 21.3%, 5.3%, and 8.0%, when measured preoperatively, on postoperative day 1, and on postoperative day 2, respectively. The LDH levels were only associated with DSS in univariate analysis when measured preoperatively (HR 2.46, 95 % CI 1.24–4.88, P = 0.01). In multivariable analysis, preoperative LDH lost its significant association with DSS (HR 1.48, 95 % CI 0.68–3.23, P = 0.33). (Table 2)

Because preoperative measurement of both S-100B and LDH showed the strongest association with melanoma prognosis, further analysis was performed on all 119 patients who all had complete preoperative biomarker data.

Table 2. Biomarkers LDH and S-100B levels on different time points and their association with melanoma prognosis in 75 patients

Characteristic	n	(%)	DFS Univariate HR (p)	DFS Multivariable[a] HR (p)	DSS Univariate HR (p)	DSS Multivariable[b] HR (p)
Preoperative LDH						
Normal	59	(78.7)	1		**1**	1
Elevated	16	(21.3)	1.61 (0.14)		**2.46 (0.01)**	1.48 (0.33)
LDH day 1						
Normal	71	(94.7)	1		1	
Elevated	4	(5.3)	1.33 (0.63)		2.04 (0.24)	
LDH day 2						
Normal	69	(92.0)	1		1	
Elevated	6	(8.0)	1.20 (0.72)		1.85 (0.25)	
Perioperative LDH change						
Became normal	12	(16.0)	1		1	1
Remained elevated	4	(5.3)	0.88 (0.84)		1.02 (0.98)	1.50 (0.75)
Became elevated	2	(2.7)	0.62 (0.66)		0.71 (0.75)	1.10 (0.93)
Remained normal	57	(76.0)	0.16 (0.60)		**0.40 (0.02)**	0.73 (0.47)
Preoperative S-100B						
Normal	48	(64.0)	**1**	**1**	**1**	**1**
Elevated	27	(36.0)	**3.08 (<0.001)**	**2.55 (0.007)**	**3.33 (0.001)**	**2.81 (0.01)**
S-100B day 1						
Normal	61	(81.3)	**1**	**1**	1	
Elevated	14	(18.7)	**2.68 (0.003)**	**2.45 (0.01)**	1.63 (0.23)	
S-100B day 2						
Normal	68	(90.7)	**1**	**1**	**1**	**1**
Elevated	7	(9.3)	**5.94 (<0.001)**	**3.80 (0.01)**	**3.93 (0.005)**	**3.76 (0.04)**
Perioperative S-100B change						
Became normal	22	(29.3)	1	1	1	1
Remained elevated	5	(6.7)	**5.69 (0.001)**	**3.39 (0.04)**	1.82 (0.31)	2.40 (0.23)
Became elevated	2	(2.7)	1.08 (0.94)	1.32 (0.80)	2.07 (0.49)	3.28 (0.30)
Remained normal	46	(61.3)	**0.37 (0.002)**	**0.42 (0.02)**	**0.32 (0.002)**	**0.35 (0.02)**

[a] Hazard ratio for DFS adjusted for presence of ulceration, LN ratio, and extranodal growth.
[b] Hazard ratio for DSS adjusted for sex, presence of ulceration, LN ratio, and extranodal growth.
Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LDH, lactate dehydrogenase.

DFS and DSS rates according to strongest predictive S-100B and LDH measurement

According to preoperative S-100B levels, 5-year DFS was 37.8% and 5-year DSS was 47.4% for patients with normal preoperative levels, which was significantly better than the 5-year DFS of 6.6% and the 5-year DSS of 28.3% for patients with elevated S-100B levels (Table 3 and Figure 1).

Although no significant associations with DFS and DSS were found for LDH levels, some differences in survival percentages were seen between patients with normal and elevated preoperative LDH levels. In patients with normal preoperative LDH levels 5-year DFS was 27.1% and 5-year DSS was 48.0% compared to 18.6% and 20.5% for patients with elevated LDH levels (Table 3 and Figure 2).

Multivariable analysis of clinicopathological and biomarker characteristics associated with DFS and DSS

In 119 patients, multivariable analysis revealed presence of ulceration (HR 1.93, 95 % CI 1.19–3.13, P = 0.008), higher LN ratio (HR 1.01, 95 % CI 1.00–1.02, P = 0.007), and preoperative elevated S-100B levels (HR 2.04, 95 % CI 1.26–3.31, P = 0.004) to be independent predictors of decreased DFS. For DSS, male gender (HR 1.93, 95 % CI 1.10–3.39, P = 0.02) and preoperative elevated S-100B levels (HR 1.82, 95 % CI 1.02–3.22, P = 0.04) revealed to be only independent predictors of worse prognosis. Preoperative LDH levels did not show a significant association with DFS and DSS on multivariable analysis. (Table 3)

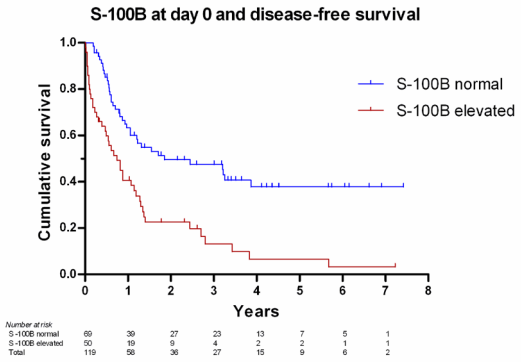
Table 3. Multivariable Cox regression analysis of prognostic significance of preoperative biomarker values in 119 melanoma patients undergoing therapeutic lymph node dissection

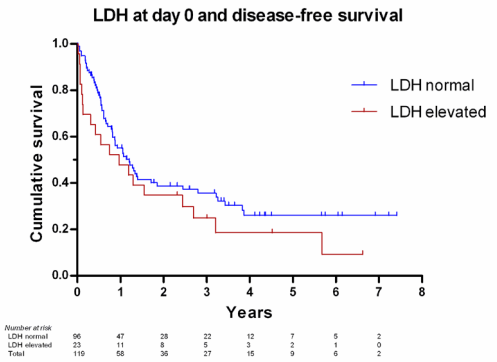
	DFS				**DSS**			
Preoperative biomarker	**3-year** %	**5-year** %	**Multivariable[a]** HR (95%CI)	**p**	**3-year** %	**5-year** %	**Multivariable[b]** HR (95%CI)	**p**
LDH								
Normal	37.2	27.1	1		55.4	48.0	1	
Elevated	24.8	18.6	1.10 (0.63-1.91)	0.75	38.3	20.5	1.39 (0.75-2.58)	0.30
S-100B								
Normal	47.5	37.8	**1**		63.3	47.4	**1**	
Elevated	13.2	6.6	**2.04 (1.26-3.31)**	**0.004**	36.3	28.3	**1.82 (1.02-3.22)**	**0.04**

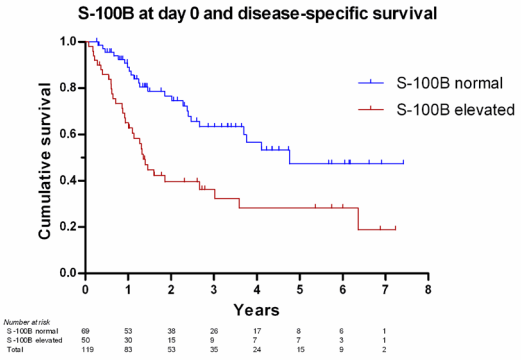
[a] Hazard ratio for DFS adjusted for presence of ulceration, LN ratio, and extranodal growth.

[b] Hazard ratio for DSS adjusted for sex, presence of ulceration, LN ratio, and extranodal growth.

Abbreviations: DFS, disease-free survival; DSS, disease-specific survival; LN, lymph node.







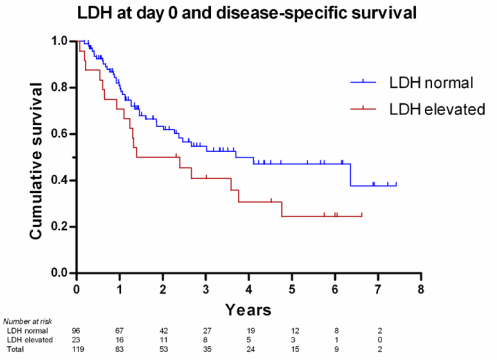


Figure 1. Disease-free and disease-specific survival according to S-100B level at day 0

Figure 2. Disease-free and disease-specific survival according to LDH level at day 0

Discussion

The present study aimed to assess and compare the prognostic significance of serum S-100B and LDH levels measured at different perioperative time points in current stage IIIB-C melanoma patients who underwent TLND with curative intent.

In the United States, the biomarker S-100B is rarely used in melanoma research and not widely accepted in melanoma care. In contrast, in Europe the marker, which seems to reflect tumor load[17], is increasingly being studied and used in clinical practice to define extent of disease in patient management. S-100B is located in the cytoplasm of melanoma cells and cell death probably results in elevated serum levels of S-100B.[6, 19] S-100B levels were already shown to be significantly correlated with the stage of disease, with normal levels in AJCC stage I and II, elevated levels in a substantial proportion of stage III patients, and highest levels in stage IV disease.[20, 21] However, S-100B seems to

lack sensitivity to justify its use as screening marker for recurrences in stage I and II disease, in an era with still limited treatment options for distant recurrences.[22] In stage IV patients S-100B levels predict response to chemotherapy[23]. For stage III melanoma, preoperatively measured S-100B was previously reported by our group to be associated with DFS[9]. However, this was studied in a much smaller cohort of 57 patients with a relatively short follow-up. Moreover, postoperative S-100B measurements, as well as LDH levels, were not analyzed and compared for their prognostic significance in that study.

The results of this study reveal that, in stage IIIB-C patients, S-100B levels show a strong association with melanoma prognosis in contrast to LDH levels. Preoperative measurements show stronger association than measurements on day 1 or 2. For DSS, male gender and preoperatively elevated S-100B were both independent predictors of worse prognosis. Moreover, preoperative measurements of S-100B showed to be the strongest independent predictor of DFS.

When preoperatively elevated, biomarker levels decreased in the majority of patients, confirming that elevated levels probably reflect regional tumor load. The best timing of both S-100B and LDH measurement to predict prognosis was the day before TLND, although LDH did not show any association with DFS or DSS in multivariable analysis. When measured preoperatively, S-100B was the strongest independent predictor of melanoma prognosis. Other measurements of prognostic significance were S-100B measured on day 2 and the change in S-100B level seen in the perioperative period. However, the latter seems predominantly an effect of the preoperative S-100B measurement, because differences were especially found between patients who had S-100B levels that remained normal and patients who had levels that became normal (i.e. were elevated preoperative). S-100B levels that remained elevated after nodal dissection in 5 patients probably indicate occult distant disease missed by preoperative FDG-PET/CT screening or any residual regional tumor load, which accounts for the decreased DFS of those patients (Table 2). Strangely, these patients did not suffer a decreased DSS. Maybe the elevated S-100B levels lead to closer monitoring in follow-up and possibly earlier aggressive surgical or medical treatment of recurrences.

The most obvious cause for the strong prognostic value of preoperative S-100B values is the representation of melanoma tumor load.[18] In addition, a second way in which S-100B levels could be linked with melanoma prognosis is outlined by some recent studies.[24,25] These studies suggest that the presence of an elevated S-100B level itself induces disease progression by suppressing the p53 tumor suppressor protein. Based on the present data, however, we are not able to determine which of those two theories is (most) responsible for the prognostic value of S-100B levels.

Other studies that compared the prognostic significance S-100B and LDH were predominantly conducted in melanoma patients with distant metastases (AJCC stage IV). While some of those studies found both S-100B and LDH to be strong prognostic factors[21, 26] and one study found LDH to be the strongest predictor of stage IV melanoma prognosis[27], other studies demonstrate that S-100B is the strongest prognostic factor and superior to LDH in patients with distant metastases[28-31].

A limitation of the present study, which also shows superiority of S-100B over LDH for estimation

of melanoma prognosis, is the limited number of patients (n=75) with complete biomarker data for both S-100B and LDH. This disabled comparison of the prognostic significance of the biomarkers in all 119 patients. However, this is the only available optimally PET-CT staged cohort of stage IIIB-C melanoma patients in which perioperative S-100B and LDH levels were compared for their prognostic value. Also, the heterogeneity in treatment modalities used in case of a recurrence, as well as the recent introduction of new treatments for stage IV melanoma, could have influenced the DSS survival data, making interpretation of the associations with DSS more complicated than interpretation of DFS data.

Future perspectives, if the present results are confirmed in larger series, comprise more accurate staging of melanoma patients with nodal macrometastases by integration of the biomarker S-100B in melanoma systems like the AJCC staging manual. Moreover, patients with nodal macrometastases who are burdened with a poor prognosis, as indicated by preoperatively elevated S-100B levels, could be selected for new trials using adjuvant or neoadjuvant medical treatment with new promising agents like ipilimumab and vemurafenib.[12,13] Selection of patients who are most likely to benefit from these drugs seem profitable, before administering these potentially toxic and still very expensive systemic drugs to stage III patients. In addition, it seems logical to include the S-100B biomarker as a stratification factor in new trials that investigate (neo)adjuvant treatments in stage IIIB–C melanoma patients.

In conclusion, the S-100B level measured preoperatively is one of the most important independent predictors of the prognosis and superior to LDH in patients undergoing TLND for AJCC stage IIIB-C melanoma.

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PART III

Feasibility of complete resection in stage IV melanoma

Chapter 8

Stage IV melanoma: completely resectable patients are scarce

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ABSTRACT

Introduction. In melanoma, about one in five patients develops distant metastases and suffers a very poor prognosis. Common treatment options comprise surgery, systemic medical therapy, and radiotherapy, depending on the number, location, and the resectability of distant metastases. Previous studies suggested that surgery should be the first choice of treatment whenever complete surgical removal is feasible. However, the proportion of patients that are candidates for this approach is not clear. The aim of the present study was to evaluate the extent of disease and resectability of melanoma patients presenting with stage IV disease at our institute.

Methods. All melanoma patients diagnosed with stage IV between January 2011 and August 2012 were assessed for extent and resectability of their disease.

Results. About half of 70 assessed patients had seven or more metastases at diagnosis, whereas 13 patients had only one metastasis. The vast majority (n=55, 78.6%) was ineligible for complete surgical resection. Six patients did receive complete surgery as initial stage IV treatment and in 9 patients incomplete surgery was performed. Widespread disease (n=44) and unresectable metastasis (n=11) were the most common reasons for refraining from complete surgery.

Conclusion. The results of the present study show that only a small proportion of patients diagnosed with stage IV melanoma are candidates for complete surgical resection with curative intent in our institution.

Introduction

In melanoma, about one in five patients develops distant metastases and suffers a very poor prognosis. These patients are classified as stage IV according to the American Joint Committee on Cancer (AJCC) staging manual. The one-year survival rate of patients diagnosed with stage IV melanoma varies between 33% and 66%, depending on lactate dehydrogenase (LDH) level and the location of the metastases.[1]

For stage I, II, and III melanoma, treatment regimens are well defined and consist of surgical resection of the primary melanoma and nodal metastases if present.[2, 3] For stage IV melanoma different treatment strategies are practicable. Depending on the number, location, and the resectability of distant metastases, common treatment options comprise surgery, systemic medical therapy, and radiotherapy.

In previous studies, the best survival rates have been found for stage IV patients who underwent complete surgical removal, i.e. total resection of all radiographic and clinically evident metastases. Small retrospective series have established that patients in whom complete surgical removal is feasible have a 5-year survival rate of 15-28%[4-9], which is superior to the 5-10% found for patients who receive systemic medical therapy[10, 11]. The prospective series of the Southwest Oncology Group showed a 25% 5-year survival in 64 patients whose metastases had been completely resected[12]. Even better survival rates have been found during the MMAIT-IV trial, which combined surgery with immunotherapy: 5-year survival was 40-45%[13]. These results suggest that surgery should be the first choice of treatment for stage IV melanoma whenever complete surgical removal is feasible.

After analysis of 291 stage IV patients in the Multicenter Selective Lymphadenectomy Trial (MSLT-I), which also suggested superiority of surgery over systemic medical therapy as initial treatment for distant melanoma[14], a phase II trial was launched by Morton et al in 2009. This multicenter randomized trial initiated by the John Wayne Cancer institute (JWCI) aimed to compare surgery and systemic medical therapy as initial treatment for completely resectable stage IV melanoma, and additionally planned to study the effect of adjuvant immunotherapy.[15] The inclusion criteria of this trial required patients to have distant disease that could be completely surgically removed.

In our experience however, most stage IV melanoma patients are treated with systemic medical therapy despite the intention to perform surgery whenever feasible. Therefore, we hypothesized that the incidence of completely resectable stage IV melanoma patients in our patients is low.

The present study aimed to evaluate the extent of disease and resectability of melanoma patients presenting with stage IV disease at our institute, in order to establish the incidence of completely resectable stage IV melanoma and to gain insight in factors that impede complete resection.

Methods

All consecutive melanoma patients with stage IV melanoma diagnosed at and referred to the Department of Surgical Oncology of the University Medical Center Groningen (UMCG), the Netherlands, between January 2011 and August 2012, were included in this study. Also, stage IV patients referred to the Department of Medical Oncology who were considered for surgery and therefore presented in a multidisciplinary conference were included. The UMCG is a tertiary referral center for melanoma patients and covers the north-eastern part of the Netherlands (Groningen, Friesland, Drenthe, Overijssel: 2,860,000 inhabitants) for specialized melanoma care. The Department of Surgical Oncology is visited by approximately 200 new melanoma patients annually.

At stage IV diagnosis, the extent and resectability of distant metastases and patient eligibility for JWCI stage IV trial was assessed. All patients were staged and their extent of disease determined by PET/CT or CT scanning and measurement of serum LDH and S-100B levels, except for patients who needed emergency surgery. Brain MRI was not routinely performed. Stage IV diagnosis was confirmed by histopathological analysis whenever possible. Extent of disease, resectability and initial treatment modality were determined in a multidisciplinary melanoma conference, attended by a radiologist, a pathologist, a surgical oncologist, a medical oncologist, and a radiotherapist.

Details of the patients, their initial stage of disease, the extent of disease at stage IV diagnosis, stage IV treatment, and reason why surgery was not performed were collected in a database. Unresectable disease was defined as one or more metastases that could not be surgically removed due to their relation with vital structures. Widespread disease was defined as seven or more metastases or involvement of four or more organs. LDH was considered elevated when the level was above 375 U/L (1.5x the upper limit of normal in our center).

Statistics

Frequencies and percentages were used for data presentation. Differences in estimated survival rates were analyzed using Kaplan-Meier curves and the Log Rank test with a significance level of 5%. Survival time was calculated from the date of stage IV diagnosis to the date of death. Statistical analysis was performed using the SPSS software package (SPSS 20.0, Chicago, Illinois, USA).

Results

Characteristics

A total of 70 patients were diagnosed with stage IV melanoma, of which 42 were male. The median age at stage IV diagnosis was 56.2 (range 19.2-82.6) years. The median time interval between primary melanoma and diagnosis of distant metastasis was 3.3 (range 0-23.6) years. According to the AJCC staging manual, the vast majority of patients suffered M1c disease (Table 1).

Table 1. Characteristics of 70 melanoma patients at stage IV diagnosis

Characteristic	n	(%)
Sex		
Female	28	(40.0)
Male	42	(60.0)
Age		
<50	22	(31.4)
50-64	24	(34.3)
65+	24	(34.3)
Initial AJCC stage		
I	7	(10.0)
II	21	(30.0)
III	23	(32.9)
IV	9	(12.9)
Unknown	10	(14.3)
M class of distant disease		
M1a	3	(4.3)
M1b	5	(7.1)
M1c	62	(88.6)

Abbreviation: AJCC, American Joint Committee on Cancer.

Table 2. Extent of stage IV melanoma at time of diagnosis

Extent of distant disease	n	(%)
Number of involved organs		
1	28	(40.0)
2	10	(14.3)
3	19	(27.1)
≥4	13	(18.6)
Number of metastases		
1	13	(18.6)
2	5	(7.1)
3	7	(10.0)
4	5	(7.1)
5	4	(5.7)
6	2	(2.9)
≥7	34	(48.6)
Location involved*		
Brain	20	(28.6)
Bone	13	(18.6)
Lung	37	(52.9)
Abdominal	42	(60.0)
(Sub)cutaneous	22	(31.4)

*Various patients had more than one location involved.

Extent of distant disease

Most patients had two or more organ sites affected by metastases and thirteen patients had four or more organs involved. In 28 patients (40.0%) only a single organ was affected by metastases (Table 2). Most frequently, the latter group of patients had brain (n=8), pulmonary (n=7), and abdominal involvement (n=9).

Overall, about half of patients had seven or more metastases at diagnosis, whereas thirteen patients had only one metastasis found. The abdominal organs and lungs were the most frequently affected by metastases. (Table 2)

Surgery as initial treatment stage IV

The vast majority of patients (n=55, 78.6%) was ineligible for complete surgical resection. Six patients did receive complete surgery as initial stage IV treatment, and in nine patients incomplete surgery was performed. Widespread disease (n=44) and unresectable metastasis (n=11) were the most common reasons for refraining from complete surgery. (Table 3)

The six patients who underwent complete surgical resection exhibited the following metastases: a single pulmonary metastasis, two subcutaneous metastases, a single metastasis in the gallbladder, a single metastasis in the small bowel, a cerebral metastasis, and a single metastasis in the skull, respectively. Incomplete surgical resection was performed for varying reasons, like an invagination, bleeding or bowel obstruction due to one of multiple abdominal metastases, debulking of a symptomatic cerebral metastasis, and diagnostic excision of a (sub)cutaneous lesion in the presence of multiple distant lesions.

Eligibility JWCI trial

As the majority of patients were not suitable for complete surgery, only six patients were screened for the JWCI stage IV trial. All six patients were found not eligible for the trial due to brain or bone involvement, inability to preoperatively confirm stage IV diagnosis by histopathology, subcutaneous metastasis of an unknown primary, elevated LDH level, or surgery already performed by other specialist before considering trial. (Table 3)

Table 3. Assessment of complete resectability and trial eligibility in 70 patients diagnosed with stage IV melanoma

Surgery as initial stage IV treatment	**n**	**(%)**
Complete surgery performed	6	(8.6)
Incomplete surgery performed	9	(12.9)
No surgery performed	55	(78.6)
Reason refrained from complete surgery: n=64		
Widespread disease	44	(62.9)
Unresectable metastases	11	(15.7)
Brain involvement	7	(10.0)
Patient in poor condition	1	(1.4)
Unknown	1	(1.4)
Reason not eligible for JWCI trial: n=6		
Brain/bone involvement	2	
No preoperative histopathology possible	1	
Subcutaneous metastasis of unknown primary	1	
Physician unaware of trial	1	
Elevated LDH level	1	

Abbreviations: JWCI, John Wayne Cancer Institute; LDH, Lactate dehydrogenase.

Survival according to initial stage IV treatment

The overall median survival was 14.6 months and the estimated 1-year survival rate was 51.0%. The one-year survival rates of patients who were treated by surgery, systemic medical therapy, radiotherapy and no antitumor therapy at al were compared. Patients who were not treated for stage IV melanoma had a significantly worse estimated one-year survival than patients that were treated with a type of antitumor therapy (0% vs 55.5%, p<0.001). There seemed to be no significant survival differences between the different stage IV treatment modalities, although small groups and limited follow-up make this comparison difficult. (Figure 1) The one-year survival rates were 75%, 49%, and 80% for surgery, systemic medical therapy, and radiotherapy, respectively (p=0.70). (Table 4)

Table 4. Survival from diagnosis according to performed treatment modality

Initial stage IV treatment	n	One-year survival
Surgery		75%
Complete surgery	6	
Incomplete surgery	2	
Incomplete surgery + SMT	*7*	
Systemic medical therapy		49%
DTIC	13	
DTIC + BRAF	14	
BRAF only	13	
DTIC + Ipilimumab	8	
Radiotherapy		80%
Radiotherapy alone	6	
Radiotherapy + SMT	*15*	
No stage IV therapy	8	0%

Abbreviations: SMT, systemic medical therapy; DTIC, dacarbazine; BRAF, vemurafinib.

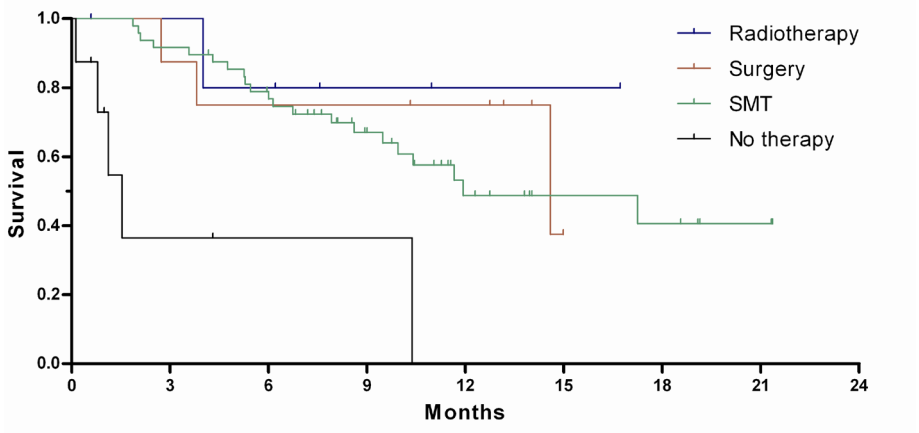

Figure 1. Stage IV survival according to performed initial treatment modality

Discussion

Stage IV melanoma is still difficult to cure and suffers a poor prognosis. So far, surgery is almost the only treatment that can provide cure. Survival rates are promising in a selected patient category in which complete surgical resection is possible.

The results of the present study reveal that only a small proportion of patients qualifies for complete surgery at time of stage IV diagnosis. Less than 10% of patients who presented with stage IV melanoma at our institution had completely resectable disease.

Higher rates of resectability found in previous studies[5, 8, 14] might be due to earlier detection of distant disease. In the Netherlands, current guidelines, which are also practiced at our institution, only recommend diagnostic imaging in follow-up if distant disease is suspected because of present clinical signs, which is the most minimalistic approach compared to other countries.[16] Melanoma guidelines in Germany[17] recommend usage of ultrasound, chest X-rays, and biomarkers in follow-up, which could account for the 25% of resectable patients found by Meyer et al[8]. Also, patients who participate in clinical trials like MSLT-I, like those in the study of Howard et al.[14], could receive a more thorough follow-up than patients who are treated in the regular follow-up. This more intense follow-up could account for earlier detection of distant disease, resulting in higher resectability rates.

Melanoma biomarkers S-100B and LDH could even further narrow the selection of patients who could potentially benefit from complete surgical resection. A study of Weide et al. revealed that the great beneficial effect of complete metastasectomy on survival was only found in stage IV patients who had both normal S-100B and LDH levels.[18] If one of the two biomarkers was elevated, which was most frequently S-100B, the survival benefit of complete metastasectomy nearly vanished. If both S-100B and LDH were elevated, there was no survival benefit at all for patients that underwent complete metastasectomy compared to other therapies. Therefore, we hypothesize that stage IV melanoma patients with elevated S-100B levels, as an indicator of extensive metastatic spread, will not benefit from complete metastasectomy, particularly if LDH levels are elevated too.

The 1-year survival rate of 51.0% and median survival of 14.6 months found for stage IV disease in the present study is similar to rates reported in literature.[1] Although median survival rates did not differ between the various initial treatment modalities, one cannot draw definite conclusions about treatment effectiveness because of the low number of patients, limited follow-up, and the presence of confounding by indication.

The multicenter randomized trial initiated by the JWCI in 2009 aimed to definitively determine which initial treatment modality is superior for resectable stage IV melanoma. However, low accrual of patients resulted in termination of the trial in September 2012. This trial termination underscores the findings of the present study.

In conclusion, the results of the present study show that only a few of the patients diagnosed with stage IV melanoma are candidates for complete surgical resection. Limited available evidence suggests better survival following a surgical approach for this highly selected group of patients.

If future studies confirmed the superiority of surgery above systemic medical therapy as initial treatment for resectable stage IV disease, it would apply to a highly selected group, because stage IV melanoma seems only surgically resectable in a limited proportion of patients. Patients with unresectable stage IV melanoma will need new successes obtained with combinations of surgery with adjuvant or neoadjuvant systemic medical therapies. Not only adjuvant immunotherapy, as was aimed to be studied in completely resectable patients by the JWCI trial, but also neoadjuvant treatment with new promising agents like ipilimumab and vemurafenib[19, 20] could improve the chances for curation in initially unresectable patients in the future.

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Chapter 9

Summary and conclusions

Melanoma healthcare currently encounters various challenges, on the one hand driven by its increasing prevalence and demand on healthcare resources, on the other hand originating from its unpredictable and almost incurable dissemination to distant sites. This chapter discusses the different leads generated by the present thesis that can contribute to improvement of both the efficiency of melanoma care and the curative treatment of progressive melanoma.

Bed rest after groin dissection

Lymph node dissection for stage III melanoma is accompanied by substantial morbidity, especially in case of a groin dissection.[1-4] Historically, patients were prescribed a long period of strict bed rest in an attempt to keep the complication rate as low as possible. More recently, more and more centers moved to shorter bed rest regimens to reduce the risk for venous tromboembolic events and increase cost-effectiveness. In *Chapter 2,* in which the influence of bed rest regimens on the early complication rate after groin dissections has been studied, early complications occurred in 48.5% of patients. Early mobilization after 5 days did not significantly increase the early wound complication rate compared to 10 day bed rest regimens. These results justify clinical application of a 5 day bed rest regimen and encourage exploration of the effects of a 3, 2, or even one day bed rest protocols in the future. These shorter bed rest protocols can contribute to an increase in cost-effectiveness of the groin dissection for melanoma, thereby reducing the demand on healthcare resources.

Completion lymph node dissection in sentinel-node positive melanoma patients

Since the abandoning of elective lymph node dissections for melanoma in the nineties, the sentinel lymph node biopsy (SLNB) is being used to select sentinel-node positive patients for completion lymph node dissection (CLND). However, still 80% of these patients have no metastases found in the lymph nodes that are removed by CLND, so called non-sentinel nodes (NSNs). In *Chapter 3* predicting factors for NSN positivity have been identified and the validity of the previously proposed non-sentinel node risk score (N-SNORE) has been assessed. Primary melanoma regression and the size of the largest sentinel node metastasis revealed to be independently associated with NSN positivity. After a slight modification, the N-SNORE scoring system has proved to provide a significant stratification of risk for NSN positivity. The selection of high risk patients using this scoring system could contribute to a more focused application of CLND in sentinel-node positive melanoma patients and lower unnecessary morbidity and costs.

Currently pending international trials are studying alternative treatment regimens for sentinel-node positive patients. The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) by Morton et al.[5] compares CLND with nodal observation using ultrasound and performing a therapeutic lymph node dissection (TLND) only if nodal metastases become clinically manifest. The EORTC MINITUB registration study[6] explores the efficacy of CLND omission in patients with minimal tumor burden in the sentinel node.

If MSLT-II reveals that immediate CLND is superior to nodal observation for a subgroup of patients, strict patient selection will improve the quality of the treatment regimen for sentinel-node positive patients. Combining different independent predictors for NSN positivity will result in the most accurate selection, irrespective of whether the goal is to select patients for CLND omission or CLND performance. The use of melanoma biomarkers S-100B and Lactate dehydrogenase (LDH) for this patient selection has been explored in *Chapter 4*. This chapter has revealed that the biomarker S-100B is a strong predictor of NSN positivity and thus can complement risk scores to select sentinel-node positive patients for CLND omission in the future.

Sentinel lymph node biopsy

SLNB has been widely accepted as an important prognostic procedure for patients with a melanoma having a Breslow thickness larger than 1 mm. SLNB with CLND for sentinel-node positive patients even seems to improve survival compared to nodal observation using ultrasound and therapeutic lymph node dissection when a metastasis becomes clinically apparent.[7] In spite of these capabilities of SLNB, *Chapter 5* reveals that still 75% of Dutch medical specialists do not consider the procedure as a standard diagnostic procedure for melanoma. They thereby agree with the content of the 2005 national guideline, which states that this procedure should be reserved for patients who want to be optimally informed about their prognosis. Adjustment of both the Dutch medical specialists' attitude and the Dutch guideline will be required if survival benefit through SLNB is established by pending trials.

Follow-up

The overall prevalence of melanoma patients continues to increase due to rising incidence rates and improved treatment outcomes. This has resulted in a rising demand on health care resources with more and more patients needing treatment and subsequent follow-up visits.[8] The frequency of follow-up visits has been widely debated for melanoma, but neither scientific evidence nor international consensus does exist. Overall, high frequency follow-up is currently recommended in countries with the highest melanoma incidence.[9] In *Chapter 5* the opinions of Dutch medical specialists reveal that the high-frequency schedules, as described by the current national melanoma guideline, could be reduced according to a substantial proportion of specialists. Reducing the frequency of follow-up schedules will partially solve the problem of the rising demand on healthcare resources.

In order to obtain scientific evidence to establish new melanoma follow-up schedules, our center prospectively studies the feasibility and safety of a reduced follow-up schedule in the pending multicenter MELFO trial.[10, 11]

Nodal metastases

The regional control and survival of melanoma patients who develop clinically detectable nodal metastases is improved by performance of a TLND with or without adjuvant radiation therapy.[12-17] Even despite accurate preoperative staging by PET/CT scanning 5-year survival rates after TLND remain unsatisfactory: 29-52%. In *Chapter 6* it is demonstrated that the anatomical site of nodal macrometastasis is an important predictor of this prognosis. Patients who undergo a TLND for nodal metastases in the neck were found to have a better disease-specific survival compared to axillary and groin sites.

Elaborating on previous studies that have shown the prognostic capacity of the preoperatively measured S-100B[18], *Chapter 7* has compared the prognostic impact of biomarkers S-100B and LDH and has determined the best timing of their measurement in stage IIIB-C melanoma. It showed that preoperatively S-100B is, in contrast to LDH, one of the most important independent predictors of melanoma prognosis in patients undergoing TLND for nodal macrometastases. These preoperative measured S-100B values enable more accurate staging of melanoma patients with nodal macrometastases when incorporated in melanoma staging systems. Moreover, patients with nodal macrometastases who are burdened with a poor prognosis, as indicated by preoperatively elevated S-100B levels, could be selected for new trials using adjuvant or neoadjuvant systemic medical treatment with new promising agents like ipilimumab and vemurafenib[19, 20].

Distant metastases

Stage IV melanoma is still difficult to cure and patients with distant metastases suffer a poor prognosis. So far, surgery seems the only treatment that can provide a cure. Survival rates are promising in the selected patient category in which complete surgical resection of all distant metastases is possible. However, as was established in *Chapter 8*, complete surgical resection of all metastases is only feasible in a small proportion of stage IV melanoma patients. If future studies confirmed the superiority of surgery above systemic medical therapy as initial treatment for resectable stage IV disease, it would only apply to this highly selected group. Patients with unresectable stage IV melanoma will need new successes obtained with combinations of surgery with adjuvant or neoadjuvant systemic medical therapies.

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Chapter 10

Nederlandse samenvatting en conclusies

De zorg voor melanoompatiënten staat voor een aantal uitdagingen. Aan de ene kant zorgt de gestaag stijgende prevalentie van het aantal melanoompatiënten voor een moeilijk te vervullen vraag naar zorgmiddelen. Aan de andere kant blijft uitzaaiing van het melanoom naar plaatsen elders in het lichaam vrij onvoorspelbaar en bijna niet te genezen. In dit proefschrift werden studies beschreven die kunnen bijdragen aan de verbetering van zowel de efficiëntie van de melanoomzorg, als de behandeling en preventie van uitzaaiingen van het melanoom. In dit hoofdstuk worden de verschillende aanknopingspunten die dit proefschrift voortbrengt op een rij gezet en hun bijdrage aan de verbetering van de behandeling van melanoompatiënten besproken.

Bedrust na lymfeklierdissectie

Een lymfeklierdissectie voor stadium III melanoom gaat gepaard met een aanzienlijke morbiditeit, vooral in het geval van de liesklierdissectie.[1-4] Oorspronkelijk werd patiënten na deze procedure langdurig strikte bedrust voorgeschreven in een poging wondcomplicaties te beperken. Tegenwoordig zijn veel centra overgestapt naar een kortere periode van bedrust, om zo het risico op tromboembolische events te beperkten en de kosteneffectiviteit te vergroten. *Hoofdstuk 2*, waarin de invloed van bedrust op het optreden van vroege wondcomplicaties na liesklierdissectie werd onderzocht, liet bij 48,5% een opgetreden wondcomplicatie zien. Vroege mobilisatie na 5 dagen bedrust gaf geen hoger risico op wondcomplicaties dan mobilisatie na 10 dagen bedrust. Deze resultaten rechtvaardigen de toepassing van een 5-daags bedrust protocol en geven de mogelijkheid het effect van nog kortere bedrust verder te onderzoeken. Deze kortere bedrust protocollen kunnen zorgen voor een toename in kosteneffectiviteit van liesklierdissecties bij melanoompatiënten.

Aanvullende lymfeklierdissectie bij schildwachtklier-positieve melanoompatienten

Sinds het verlaten van de electieve lymfeklierdissecties voor het melanoom in de jaren negentig wordt de schildwachtklierprocedure gebruikt om patiënten met positieve schildwachtklieren te selecteren voor aanvullende lymfeklierdissectie. Echter, bij 80% van deze patiënten worden geen metastasen gevonden bij histologisch onderzoek van de bij aanvullende klierdissectie verwijderde klieren (zogenaamde non-sentinel nodes). In *Hoofdstuk 3* van dit proefschrift zijn voorspellende factoren voor non-sentinel node positiviteit geïdentificeerd. Tevens werd de non-sentinel node risk score (N-SNORE), die eerder in de literatuur werd beschreven, getoetst. Voorspellende factoren voor non-sentinel node positiviteit waren regressie in het primaire melanoom en de afmeting van de metastase in de schildwachtklier. De N-SNORE bleek, na een kleine aanpassing, een goede risico-inschatting te geven van de kans op het vinden van metastasen in de aanvullende klierdissectie. Het op deze wijze identificeren van laag- en hoogrisico patiënten zou minder breed toepassen van aanvullende klierdissecties mogelijk kunnen maken, en daarmee onnodige morbiditeit en kosten besparen.

Momenteel lopende internationale trials onderzoeken alternatieve behandelingsopties voor schildwachtklier-positieve patiënten. De tweede Multicenter Selective Lymphadenectomy Trial (MSLT-II) van Morton et al.[5] vergelijkt directe aanvullende klierdissectie met echografische observatie van het klierstation en uitvoeren van een therapeutische lymfeklierdissectie wanneer er lymfekliermetastasen aan het licht komen. De EORTC MINITUB registratie studie[6] onderzoekt het effect van het achterwege laten van een aanvullende klierdissectie bij patiënten met minimale tumorload in de schildwachtklier.

Als de MSLT-II studie laat zien dat directe aanvullende klierdissectie beter is dan observatie van het klierstation, dan zou patiëntselectie voor deze therapie de behandeling van schildwachtklier-positieve patiënten kunnen verbeteren. Combinatie van verschillende voorspellers van non-sentinelnode positiviteit zal de meest accurate selectie opleveren, ongeacht of het doel is patiënten te selecteren voor het uitvoeren of juist voor het afzien van aanvullende klierdissectie.

De bruikbaarheid van de biomarkers S-100B en Lactaat dehydrogenase (LDH) voor deze patiëntselectie werd onderzocht in *Hoofdstuk 4*. In dit hoofdstuk staat beschreven dat de biomarker S-100B een sterke voorspeller is van non-sentinel node positiviteit en derhalve risico scores voor non-sentinel node positiviteit kan aanvullen. Op deze manier kunnen schildwachtklier-positieve patiënten met een laag risico worden geselecteerd om hen een aanvullende klierdissectie te besparen.

Schildwachtklierprocedure

De schildwachtklierprocedure is algemeen geaccepteerd als een belangrijke prognostische procedure voor melanoompatiënten met een melanoom dikker dan 1 mm Breslowdikte. Het uitvoeren van de schildwachtklierprocedure met aanvullende klierdissectie in geval van een positieve schildwachtklier lijkt zelfs een overlevingsvoordeel op te leveren ten opzichte van echografische controle van het lymfeklierpakket en therapeutische lymfeklierdissectie wanneer er een metastase wordt gevonden.[7] Ondanks deze capaciteiten blijkt uit *Hoofdstuk 5* dat 75% van de Nederlandse medisch specialisten van mening zijn dat de schildwachtklierprocedure niet behoort tot de standaard diagnostiek van het melanoom. Zij conformeren zich aan de inhoud van de Nederlandse Richtlijn Melanoom uit 2005, waarin staat dat de schildwachtklierprocedure dient te worden gereserveerd voor patiënten die optimaal geïnformeerd willen worden over hun prognose en dat deze procedure geen deel uitmaakt van de standaard diagnostiek. Aanpassing van zowel de nationale richtlijn als de houding van Nederlandse medisch specialisten is noodzakelijk, zeker als lopende studies een echt overlevingsvoordeel laten zien van deze procedure.

Follow-up

De prevalentie van melanoompatiënten blijft stijgen door de stijgende incidentie van het melanoom en verbeterde behandelingsresultaten. Dit heeft geleid tot een stijgende vraag naar zorgmiddelen rondom het melanoom, met steeds meer melanoompatiënten die behandelingen en follow-up nodig hebben.[8] De frequentie van follow-up van melanoompatiënten is sinds lange tijd een groot discussiepunt

doordat wetenschappelijke data ontbreken en internationale studies op dit thema niet bestaan. In de landen met de hoogste melanoomincidentie wordt momenteel een hoogfrequent follow-up schema aanbevolen.[9] In *Hoofdstuk 5* werd onder andere de mening van Nederlandse medisch specialisten over follow-up onderzocht. Dit hoofdstuk laat zien dat de intensiteit van hoogfrequente follow-up schema's, zoals geadviseerd door de Nederlandse richtlijn uit 2005, zou kunnen worden verminderd volgens een groot deel van de Nederlandse medisch specialisten. Het reduceren van de intensiteit van follow-up schema's zou bijdragen aan het oplossen van de toenemende zorgvraag rondom het melanoom.

Om wetenschappelijke onderbouwing te verkrijgen voor nieuwe follow-up schema's voor melanoompatiënten onderzoekt het Universitair Medisch Centrum Groningen de toepasbaarheid en veiligheid van een gereduceerd follow-up schema in de lopende MELFO trial.[10, 11]

Lymfekliermetastasen

De regionale controle en overleving van melanoompatiënten die een klinisch detecteerbare lymfekliermetastase ontwikkelen kan worden verbeterd door het uitvoeren van een zogenaamde therapeutische lymfeklierdissectie met of zonder adjuvante radiotherapie.[12-17] Ondanks nauwkeurige preoperatieve stadiëring met behulp van een PET en/of CT scan blijft de 5-jaarsoverleving van deze patiëntencategorie teleurstellend: 29-52%. In *Hoofdstuk 6* werd aangetoond dat de anatomische lokalisatie van de lymfekliermetastase een belangrijke voorspeller is van de prognose na een therapeutische lymfeklierdissectie. Patiënten die een therapeutische lymfeklierdissectie ondergaan voor een metastase in de hals, hebben een betere melanoomspecifieke overleving dan patiënten met een metastase in de oksel of lies.

Voortbordurend op eerdere studies die de prognostische waarde van de biomarker S-100B hebben aangetoond[18], is in *Hoofdstuk 7* de prognostische impact van de biomarkers LDH en S-100B vergeleken en de optimale timing van hun meting onderzocht bij stadium IIIB-C melanoompatiënten. Preoperatief gemeten S-100B bleek, in tegenstelling tot LDH, één van de belangrijkste voorspellers van de prognose bij stadium IIIB-C melanoompatiënten die een therapeutische lymfeklierdissectie ondergingen.

Het includeren van S-100B in de huidige melanoomclassificatie zou leiden tot betere stadiëring van melanoompatiënten met lymfekliermetastasen. Bovendien kunnen melanoompatiënten die belast zijn met een slechte prognose, voorspeld door een preoperatief verhoogd S-100B level, worden geselecteerd voor nieuwe trials met (neo)adjuvante therapie met nieuwe systemische middelen zoals ipilimumab en vemurafenib.[19, 20]

Afstandsmetastasen

Stadium IV melanoom is nog altijd moeilijk te genezen en deze patiënten met afstandsmetastasen hebben een zeer slechte prognose. Tot op heden lijkt chirurgische resectie de enige behandelmodaliteit die curatie kan bewerkstelligen. In een geselecteerde patiëntencategorie waarbij complete resectie van alle metastasen mogelijk is, lijken de overlevingscijfers dan ook bemoedigend. Echter, zoals *Hoofdstuk 8* laat zien, komt minder dan 10% van alle stadium IV patiënten in aanmerking voor complete resectie van alle afstandsmetastasen. Dus als toekomstige studies de superioriteit van complete chirurgische resectie boven systemische medische therapieën zouden aantonen, zou dit alleen van toepassing zijn op een zeer klein deel van alle stadium IV patiënten. De overige patiënten die niet in aanmerking komen voor complete chirurgische resectie blijven afhankelijk van nieuwe successen die mogelijk kunnen worden behaald met combinaties van chirurgie en (neo)adjuvante toepassing van nieuwe systemische middelen.

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Chapter 11

Future perspectives

Rising incidence and costs

From an epidemiologic point of view, it is expected that the incidence of cutaneous melanoma will continue to rise in most countries.[1] In the Netherlands, not only the incidence of thin melanomas is steadily increasing, but also thick melanomas will be more frequently diagnosed in the upcoming years. It has been estimated that this increasing incidence will result in 5400 newly diagnosed melanomas in 2020, compared to 4665 in 2010. The prevalence of melanoma patients is therefore thought to be 1.5 times higher in 2020, entailing a significant rise in health care costs. In addition, the number of annual melanoma associated deaths is expected to rise from 783 in 2010 to 970 in the year 2020. [2, 3]

To combat these worrying incidence trends, primary prevention is most effective. Therefore, the importance of sun-protective behavior in skin cancer prevention, especially for children and adolescents, has already been propagated for a couple of decades. More recently, a growing number of population-based studies report an association between tanning bed use in young people and risk for melanoma.[4-6] Reducing tanning bed usage through strict legislation, as is already implemented in some countries, could flatten the rise in melanoma incidence and the entailing health care costs.

Restraining the rise in costs for melanoma care could possibly be obtained by better patient selection for surgical procedures like lymph node dissections and increasing their cost-effectiveness, for instance by reducing bed rest regimens as described in this thesis. The pending MELFO trial[7, 8] studies whether less intensive follow-up schedules for melanoma patients are feasible and safe. If so, this can create a significant reduction in the costs of melanoma care.

Prediction of outcome and patient selection

Today's attempts to gain progression in surgical oncology are not only focused on improving the quality of surgical procedures, but increasingly on prediction of outcome based on risk profiles and patient selection. As was shown in *Chapter 3 and 4* of the present thesis, completion lymph node dissection (CLND) seems to be overtreatment in about 80% of sentinel node (SN)-positive patients. In the future, predictive risk scores will become more and more important to decide whether treatments, like CLND, will be beneficial for the outcome of the individual patient. Biomarkers, like the melanoma biomarker S-100B, will be increasingly used in such risk scores, as they can provide important prognostic information. In addition, pending research is studying whether more details encoded in the (expression of) DNA in melanoma cells could be used for the prediction of outcome following systemic treatments.

Sentinel lymph node biopsy

Now that the follow-up of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) is completed, we will soon be informed about whether performance of sentinel lymph node biopsy (SLNB) improves patient survival compared to watchful waiting with ultrasound in patients with melanomas with Breslow thickness > 1 mm. Following the results of the last interim analysis, we expect a modest survival benefit after ten years of follow-up in patients who underwent SLNB.[9]

For patients with thin melanoma (< 1 mm Breslow thickness), the prognosis is not very likely to improve through SLNB because their survival is already very good and the rate of sentinel node positivity in these patients is very low. SLNB for thin melanoma in highly selected patients showed 8% SN positivity[10]. New studies will focus on the prognostic impact and survival influence of SLNB in patients with thin melanomas especially for melanomas with a Breslow thickness between 0.75 and 1 mm.

Nodal dissections

Besides moving to even further reduced bed rest regimens to increase patient comfort and cost-effectiveness of the groin dissection, a future approach that is currently being explored encompasses laparoscopic groin dissection in an attempt to reduce the rate of wound complications.[11]

New systemic therapies

Recently, a revolution is initiated by the introduction of two systemic drugs showing promising response rates in stage IV melanoma patients: ipilimumab, an anti-CTLA4 antibody, and vemurafenib, a selective inhibitor of the BRAF signaling pathway. Future research in stage IV melanoma patients will focus on simultaneous blockage of different signal transduction pathways to increase the durability of the therapeutic responses. A recently opened trial combines BRAF inhibition with MEK inhibition for this purpose[12].

Moreover, these new systemic medical agents will soon be tested as adjuvant therapy in curatively treated patients. The upcoming COMBI-AD trial will study the effect of a BRAF inhibitor combined with an MEK inhibitor on relapse-free survival in BRAF-mutation positive patients with stage IIIB-C and even IIIA melanoma.[13] Prognostic factors like S-100B, as described in this thesis, can improve patient selection for administration of these potentially harmful and expensive drugs in adjuvant setting. If these adjuvant treatments proof to be effective, these therapies could even replace CLND in sentinel node positive patients in the future.

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Appendices

List of publications

Dankwoord

Curriculum vitae

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Kevin

Groningen, april 2013

Curriculum vitae

Kevin Wevers werd geboren op 30 augustus 1985 te Nijmegen. Hij groeide op in Bemmel als oudste zoon van Ron Wevers en Ria Noordhoek en broer van Mark en Jim. Na het behalen van zijn diploma aan het Stedelijk Gymnasium te Nijmegen in 2003, studeerde hij Geneeskunde aan de Rijksuniversiteit Groningen (2003-2009).

In het laatste studiejaar volgde hij zijn semi-artsstage op de afdeling Chirurgie in de Isala Klinieken te Zwolle. Aansluitend volgde zijn wetenschappelijke stage onder begeleiding van dr. G.A. Patijn. In dit project onderzocht hij de waarde van C-reactive protein (CRP) als voorspeller voor conversie bij patiënten die een acute laparoscopische cholecystectomie ondergaan. Met de afronding hiervan werd in 2009 de artsengraad behaald. Aansluitend was hij gedurende anderhalf jaar werkzaam als ANIOS Chirurgie in de Isala Klinieken.

Gesteund en gemotiveerd door dr. E.G.J.M. Pierik startte hij begin 2011 als arts-onderzoeker een promotietraject onder begeleiding van prof. dr. H.J. Hoekstra, wat na ruim twee jaar heeft geresulteerd in dit proefschrift.

Hij werd in september 2012 aangenomen voor de opleiding Heelkunde in regio VI (opleider prof. dr. E. Heineman) en is nu sinds een half jaar werkzaam als chirurg in opleiding in het Medisch Centrum Leeuwarden (opleider dr. J.S. de Graaf).